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Review Article

Effect of ginseng and ginsenosides on attention deficit hyperactivity disorder: A systematic review

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a rapidly increasing neurodevelopmental disorder but currently available treatments are associated with abuse risk, side effects, and incomplete symptom relief. There is growing interest in exploring complementary options, and ginseng has gained attention for its therapeutic potential. This systematic review aimed to assess current evidence on the efficacy of ginseng and its active components, ginsenosides, for ADHD. Eligible studies were identified through searches of PubMed, Embase, Cochrane Library, and Web of Science, up to June 2023. The inclusion criteria included both human and animal studies that investigated the effects of ginseng or ginsenosides on ADHD. The risk of bias was assessed according to study type. Six human studies and three animal studies met the inclusion criteria. The results suggest that ginseng and ginsenosides may have beneficial effects on ADHD symptoms, particularly inattention, through dopaminergic/norepinephrinergicmodulation and BDNF/TrkB signaling. Ginseng and ginsenosides have promising potential for ADHD treatment. Due to limitations in evidence quality, such as the risk of bias and variability in study designs, larger controlled studies are essential. Integrating ginseng into ADHD management may have valuable implications for individuals seeking well-tolerated alternatives or adjunctive therapies.

Registration

The protocol of this systematic review was registered on PROSPERO (registration number: CRD42023446324)

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is a highly prevalent disorder that has detrimental effects on mental health, academic performance in children and work performance in adults. and is often accompanied by both mental illness (e.g. depression and behavioral disorders) and physical illness (e.g. obesity) [1–4]. It is characterized by persistent inattention, hyperactivity, and impulsivity, which impair neuropsychiatric function and development. According to the World Federation of ADHD International Consensus Statement which is published in 2021, the prevalence of ADHD is approximately 5.9 % in children and adolescents, and persists into adulthood in approximately 75 % of cases, with a prevalence of approximately 4.4 % in adults [5]. It has not increased in prevalence over the past three decades, although it is more likely to be diagnosed now than in previous decades due to increased recognition by clinicians [5]. In Korea, the number of patients has increased by over 92 % in 4 years, and medical expenses have increased by 130 % over 5 years [6]. In the United States (US), ADHD is one of the most common diagnoses among children aged 3–17, with a prevalence of 9.8 % [7]. ADHD diagnoses in adults has also increased significantly over the past 10 years, growing at a rate 4 times faster than that in children [8].

The use of medications that target dopamine or norepinephrine has skyrocketed in children and adolescents [9]. However, methylphenidate, the first-line medication, alleviates symptoms by inhibiting dopamine reuptake resulting in rapid symptom improvement, but requires continuous intake [10]. Concerns have emerged regarding the potential for abuse, and various side effects (e.g. headaches, growth delay due to decreased appetite, drowsiness, nausea, fatigue, hypersensitivity, and dizziness) associated with these medications [11,12]. Nevertheless, the prescription of ADHD medications has increased exponentially in recent years, posing social issues. In the US, 18 % of children aged 2–5 with ADHD, for whom behavioral therapy was recommended, are taking

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ADHD medications [7]. The prescription rates of stimulants in the US increased during 2016–2021, not only in children, but also among adolescents and adults by more than 10 %, particularly between 2020 and 2021 [13]. In Korea, the population receiving newly prescribed medications for adult ADHD has experienced a significant growth of 322 % over 4 years [14].

Ginseng is a medicinal herb that contains several active compounds, including ginsenosides that potentially contribute to the management and treatment of various diseases. Ginseng or ginsenosides may be beneficial in the treatment of neurological diseases, cardiovascular diseases, metabolic diseases, cancer, hepatic diseases, skin disorders, and immune function [15–27]. Ginsenosides have a number of benefits, including improved cognitive function [15,28]. Korean Red Ginseng (KRG), whose marker compounds are the ginsenosides Rg1, Rb1, and Rg3, has been approved by the Korean Food and Drug Administration as a supplement for improving memory. Studies exploring cognitive function, including the enhancing effect of Panax species on attention in healthy adults [29,30], have shown that ginseng and its constituents are promising therapeutic candidates for ADHD.

This study aimed to perform a comprehensive systematic review of the effect of ginseng and its derivatives on symptoms of ADHD. The study searched both human studies, such as randomized controlled trials (RCTs) and pre-post studies, and animal studies, and investigated their efficacy on the phenotypes of ADHD and its underlying mechanisms.

2. Materials and methods

2.1. Search strategy

The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROPSERO) (CRD42023446324) prior to commencing the work. Four electronic databases were searched for original studies published in English until June 30, 2023: PubMed, Embase, Web of Science, and Cochrane Library (Search strategies are shown in Appendix A). Reference lists of relevant publications were used to identify relevant research articles and reviews.

2.2. Eligibility criteria

Inclusion criteria were (i) studies that tested ginseng or its constituents and its mixture with other compounds, and (ii) studies that primarily focused on ADHD-related symptoms. Studies involving both human and animal subjects were included. The exclusion criteria were (i) studies that assessed inattention, hyperactivity, or impulsivity associated with diseases other than ADHD and (ii) book chapters, posters, theses, editorials, and conference papers.

For human studies, the primary outcome was assessment of ADHD symptoms (e.g. ADHD Rating Scale (ADHD-RS), Conners' rating scale, and Clinical Global Impression (CGI)). Neuropsychological tests (e.g. continuous performance test (CPT), Children Behavior Check List (CBCL)) and electroencephalography (EEG) were also reviewed for secondary outcomes. For animal studies, the pharmacological effects of ginseng and its constituents on ADHD-like phenotypes and biochemical analyses were included.

2.3. Data extraction

Three reviewers (YK, IC, and SC) independently screened the literature that was initially searched from the databases based on titles and abstracts. Any discrepancies between the reviewers were resolved through discussion. Basic characteristics of the studies (authors, study design, and year of publication), characteristics of the study subjects (species, sample size, average age, sex, diagnosis in human studies, and experimental models of animal studies), description of intervention and control (dose, method, and timing of ginsenoside administration), and outcome measures and their results were extracted. The study selection process is summarized in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Fig. 1).

2.4. Study risk of bias assessment

Each study was assessed by 3 independent reviewers based on the description of the study design, participant/animal, method and assay, variable assessment and control groups, and data collection procedures. For human studies, the Cochrane risk of bias assessment 2.0 tool was used to assess RCTs, and the National Institutes of Health (NIH) quality assessment tool for pre-post studies with no control group was used for single-arm trial [31,32]. We assessed the methodological quality of animal studies regarding the risk of bias based on the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) [33] and a modified scale from the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) [34]. Plots were generated using Risk-Of-Bias VISualization (robvis) package [35].

3. Results

3.1. Description of included studies

The authors searched for relevant studies examining the efficacy of ginseng on ADHD in four databases (PubMed, Embase, Cochrane Library, and Web of Science) and 7329 records were initially identified. After removing duplicates (n = 3541), the remaining records were screened for eligibility (n = 3788); 3769 records were excluded and 19 remaining records were sought for full-text retrieval. Among them, 11 did not meet the inclusion criteria and were excluded for the following reasons: reviews (n = 10) or out of topic (n = 1) (Appendix B). Additionally, a report obtained by citation searching was added (n = 1). Altogether, 9 studies were included in this review: 6 were human studies including RCTs (n = 2) and pre-post studies (n = 4), while the remaining 3 were animal studies (Fig. 1).

3.2. Characteristics of the included studies

This review included 9 studies that investigated the effects of ginseng or its constituents on ADHD or related symptoms in humans and animals. The studies were published between 2001 and 2021 and were conducted in countries such as Korea, Italy, Canada, and China. The studies varied in their study designs, sample sizes, interventions, and outcome measures and their basic characteristics are described in Tables 1–2.

3.2.1. Characteristics of the included human studies

The human studies included 2 RCTs [36,37] and 4 pre-post studies without a control group of children or adolescents [38–41]. The sample sizes of RCTs ranged from 70 to 120, and those of pre-post studies ranged from 3 to 40. Although Niederhofer allowed each participant to receive both the intervention and placebo drug in a similar format with a crossover design, we judged this study as a pre-post study as the author enrolled only 3 patients and presented only the pre-post treatment change of the intervention phase instead of comparing the values between the 2 phases [40]. The participants were predominantly male, with ages ranging from 3 to 17 years. All participants were diagnosed with ADHD based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) or fifth edition (DSM-5) criteria, except for 1 RCT that included children with subthreshold ADHD who met at least 3–5 inattentive and hyperactivity/impulsive symptoms of ADHD criteria in DSM-5 [36].

The interventions included different forms and doses of KRG alone [37,39,40], KRG in combination with omega-3 fatty acids [36,38], and a combination of *Panax quinquefolius* and *Ginkgo biloba* extracts [41]. The

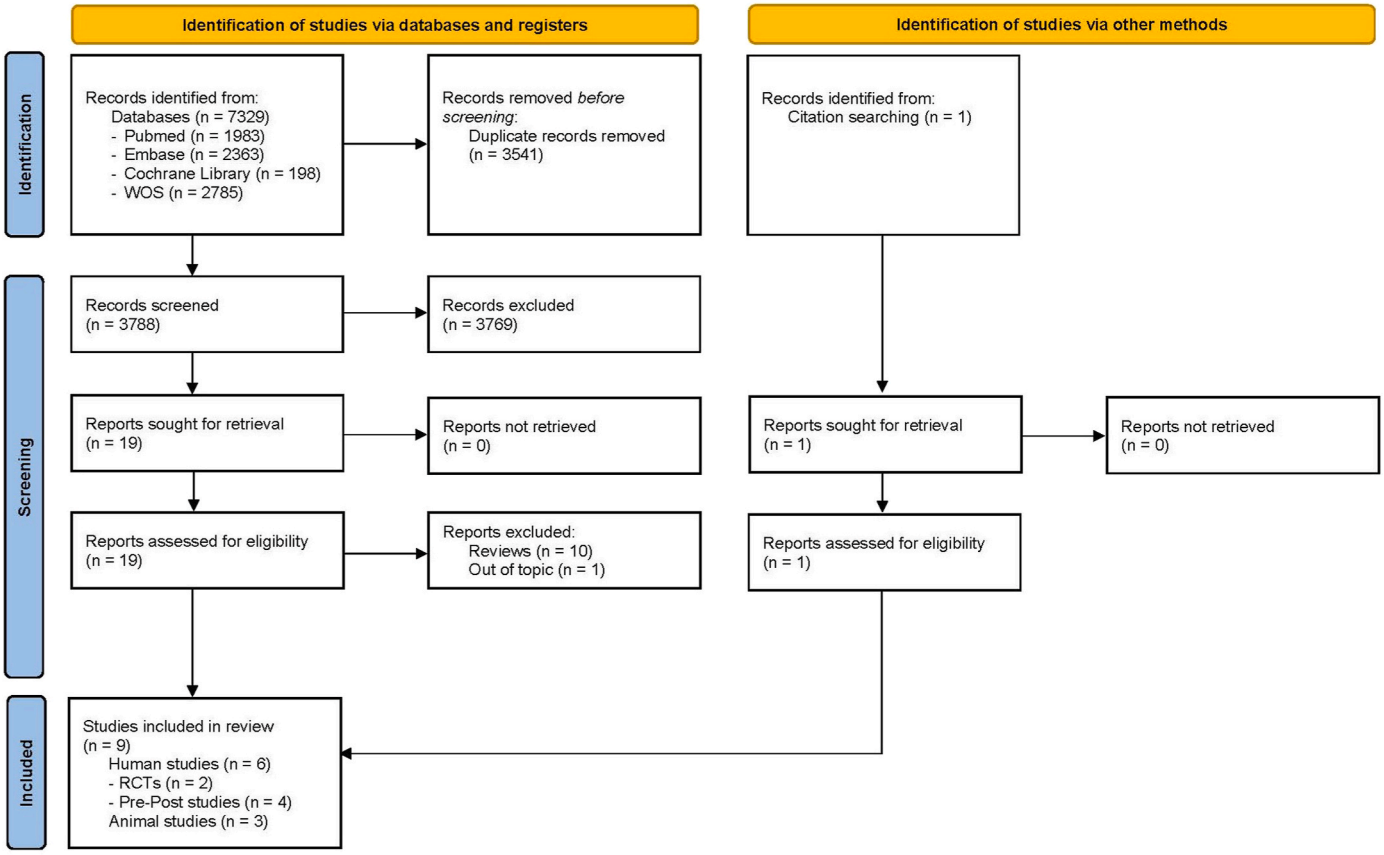

Fig. 1. Flow chart of the included studies.

daily dose of KRG was 2 g [37,39] or 500 mg [40], while 3 mg was used with 500 mg omega-3 [36,38]. The daily dose of *P. quinquefolius* was 400 mg mixed with 100 mg of *G. biloba* extract [41]. It was administered orally to all participants. All the control interventions in RCTs were placebos. The duration of the intervention ranged from 4 to 12 weeks, with most studies lasting 8 weeks.

The outcome measures included various scales and tests to assess ADHD symptoms, such as the ADHD-RS [36,38–40], CGI [38,40] and Conners' ADHD Rating Scale [39,41]. Some studies have assessed other measures related to cognitive function and emotional and behavioral problems, including the CBCL [36,39], neuropsychological tests such as computerized CPT (e.g. Advanced Test of Attention (ATA), ADHD Diagnostic System (ADS), and Conners' CPT) [36,38–40], and quantitative EEG (qEEG) [37]. Neurochemical levels of salivary cortisol and dehydroepiandrosterone (DHEA) were also tested for chronic stress [37] (Table 1).

3.2.2. *Characteristics of the included animal studies*

The 3 included animal studies examined the effects of ginseng and ginseng-related compounds on ADHD-like behavior and neurochemical changes in rat or mouse animal models, either genetically or environmentally, to demonstrate ADHD-like behaviors, and included 3 different models of ADHD: the polychlorinated biphenyl (PCB)-exposed model [42], spontaneously hypertensive rat (SHR) model [43] and neonatal hypoxia-induced hyperactivity model [44]. The sample sizes ranged from 8 to 10 subjects per group. The interventions included YY162 (ginsenoside Rg3 and terpenoid-strengthened *G. biloba*, 200 mg/kg/day, p.o.) [42], ginsenoside Rg1 (40 mg/kg/day, p.o.) [43], and KRG (200 mg/kg/day, p.o.) [44]. Two studies lasted 14 days [42,43] while the other lasted 7 days [44]. The control interventions were methylphenidate hydrochloride [42,43] or a vehicle such as distilled water [43,44] or corn oil [42]. The behavioral tests used in the included studies were open-field test (OFT) [42,44] and elevated plus-maze (EPM) [42] for hyperactivity/impulsivity, the rotarod test [44] for motor coordination, and the object-based attention test (OAT) [42] for inattention. Levels of dopamine and norepinephrine or their transporters (dopamine transporter (DAT) and norepinephrine transporter (NET)) were measured in the prefrontal cortex and striatum [42–44], along with brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) expression [42], and oxidative stress [42] (Table 2).

3.3. *Risk of bias in studies*

Different criteria were used for quality assessment to evaluate the risk of bias according to the study type.

The Cochrane risk-of-bias 2.0 tool was used for RCTs. Lee et al. reported a high risk of overall bias because per-protocol (PP) analysis was applied, although the study maintained a low risk of bias in the randomization process, missing outcome data, outcome measurement, and selection of the reported result domains [36]. Ko et al. reported a low risk of bias in the outcome measurement and selection of the reported result domains. However, as approximately 39 % of the intervention group and 43 % of the control group failed to collect EEG data, and allocation concealment was not reported, the study was judged to have some concerns regarding the risk of bias [37] (Fig. 2A).

The NIH quality assessment tool for before-after (Pre-Post) study with no control group was applied, which has 12 criteria to judge the internal validity of the studies [31]. Three studies had good ratings, as they met most of the criteria, except for 1 item owing to their small sample size [38,39,41]. However, 1 study was assessed to have poor quality as it did not enroll enough participants and reported results without appropriate statistical analysis [40] (Fig. 2B).

For animal studies, SYRCLE and CAMARADES were used to assess the risk of bias. Nam et al. showed a low risk of bias in most items, except

Table 1
Characteristics of human studies included in the systematic review of the effects of ginseng and ginsenosides on ADHD.

First author, Year	Species (Sample size (E/C))	Age range or mean age	Diagnosis	Experimental group	Control group	Outcome measure	Adverse events reported
Double-blind Randomized controlled trial							
Lee, 2021	Human (E/C = 60/60)(M/F = 79/41)	6–12 y 9.22 ± 1.77 y	Subthreshold ADHD based on DSM-5	KRG extract (combination of ginsenosides Rg1, Rb1, and Rg3) 3 mg + omega-3500 mg (EPA, 294 mg; DHA, 206 mg), p.o., 12 wk	Placebo, p.o., 12 wk	ADHD-RS↓ - Total score↓, Inattention↓, Hyperactivity n.s. CBCL↓ - ADHD, Withdrawn/depressed, Social problems, Attention problems, Rule-breaking behavior, Aggressive behavior↓ - Somatic complaints, Anxious/depressed, Thought problems n.s. ATA, AVLT, CCTT, SWCT n.s.	None
Ko, 2014	Human(E/C = 33/37)(M/F = 44/26)	6–15 y E: 10.94 y C: 10.86 y	ADHD based on DSM-IV	concentrated KRG extract 1000 mg, p.o., bid, 8 wk	Placebo, p.o., bid, 8 wk	Inattention and hyperactivity/impulsiveness scale score - Inattention↓, Hyperactivity↓ qEEG theta/beta ratio↓ Salivary cortisol, salivary DHEA n.s.	None
Pre-post studies							
Lee, 2020	Human (40)(M/F = 31/9)	6–12 y 8.00 ± 1.45 y	ADHD based on DSM-5	KRG extract (combination of ginsenosides Rg1, Rb1, and Rg3) 3 mg + omega-3500 mg (EPA, 294 mg; DHA, 206 mg), p.o., 12 wk	–	ADHD-RS - Total score↓, Inattention↓, Hyperactivity↓ CGI-Severity↓ ATA - Visual-Commission error, Reaction time↓/Omission error, Reaction time variability n.s. - Auditory-Omission error, Commission error, Reaction time, Reaction time variability n.s. AVLT↑, CFT↑, SCWT↑	Transient headache (n = 1)
Lee, 2011	Human (18)(M/F = 18/0)	6–14 y	ADHD based on DSM-IV	KRG capsule 1,000 mg, p.o., bid, 8 wk	–	ADS - Omission error, Response time SD↓ - Commission error, Response time n.s. Conners Rating Scale↓ ADHD-RS - Total score, Inattention, Hyperactivity n.s. Learning Disorder Scale n.s. CBCL n.s., SAIC↓, TAIC n.s., Kovac's CDI n.s. KPI-C - Physical development, Social dysfunction↓	None
Niederhofer, 2009	Human (3/0 (crossover design))(M/F = 3/0)	14–17 y	Inattention type ADHD based on DSM-IV	*Panax ginseng* extract 250 mg tablet (27–30 % ginsenosides), p.o., bid, 4 wk and then placebo, p.o., bid, 4 wk	Placebo	ADHD-RS - Total score↓, Inattention↓, Hyperactivity↓ CGI-Improvement↑ CPT - Omission error↔, commission error↓ (Statistical significance not reported)	Mild sedation (n = 1)
Lyon, 2001	Human (36)(M/F = Not reported)	3–17 y 10.2 ± 3.7	ADHD based on DSM-IV	*Panax quinquefolius* 200 mg + *Ginkgo biloba* extract 50 mg, capsule, p.o., bid, 4 wk	–	Conners' Parent Rating Scale − 7 symptom areas↓ − 7 global attributes↓	Being more emotional and more impulsive (n = 1) Being more hyperactive and more aggressive (n = 1)

ADHD, Attention Deficit Hyperactivity Disorder; ADHD-RS, Attention Deficit Hyperactivity Disorder-Rating Scale; ADS, ADHD Diagnostic System; ATA, Advanced Test of Attention; AVLT, Auditory Verbal Learning Test; C, Control group; CBCL, Child Behavior Check List; CCTT, Children's Color Trail Test; CDI, Children's Depression Inventory; CFT, Complex Figure Test; CGI, Clinical Global Impression; CPT, continuous performance test; DHA, docosahexaenoic acid; DHEA, Dehydroepiandrosterone; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; E, Experimental group; EPA, Eicosapentaenoic acid; F, Female; KPI-C, Korean Personality Inventory for Children; KRG, Korean Red Ginseng; M, Male; n.s., not significant;

qEEG, Quantitative electroencephalography; SD, Standard deviation; SWCT, Stroop Word Color Test; SAIC, State Anxiety Inventory for Children; TAIC, Trait Anxiety Inventory for Children.
Statistical analysis of outcomes in RCTs are between-group difference.
Statistical analysis of outcomes in pre-post studies are within-group difference.

Table 2
Characteristics of animal studies included in the systematic review of the effects of ginseng and ginsenosides on ADHD.

First author, Year	Species (Sample size (E/C))	Age range or mean age	Model	Weight	Experimental group	Control group	Outcome measure - Behavioral tests	Outcome measure - Biochemical analysis
Animal studies								
Nam, 2014	ICR mice (E/C1/C2/C3 = 10/10/10/10) (M/F = 20/20)	Postnatal day 21	PCB-exposed model	Not reported	Ginsenoside Rg3 + terpenoid-strengthened *Ginkgo biloba* 200 mg/kg, p.o., qd, 15 d	C1 PCB + Vehicle, 15 d C2 PCB + Methylphenidate 5 mg/kg, i.p., qd, 15 d C3 PCB + K252a 0.1 or 0.3 mg/kg, i.p., qd, 15 d	Open-field test - total distance moved↓, entry latency to central zone↑ (vs C1, C3), distance moved in central zone↓ (vs C1) Elevated plus-maze - number of open arm entries↓, Time spent in open arm↓ (vs C1, C3) Object-based attention test↑ (vs C1, C3)	prefrontal cortex BDNF↑, *p*-TrkB↑ (vs C1, C3) DAT↑, NET↑ (vs C1, C3) ROS↓, Protein carbonyl↓, MDA↓ (vs C1, C3)
Hu, 2012	Rats (E/C1/C2/C3 = 8/8/8/8)(M/F = 16/0)	11 wk	Spontaneously hypertensive rats (SHR) model	E: 285–310 g C: 180–220 g	Ginsenoside Rg1 40 mg/kg, p.o., qd, 14 d	C1 WKY rats C2 SHR rats C3 SHR + Methylphenidate 5 mg/kg, p.o., qd, 14 d	None	*Prefrontal cortex* Dopamine↑, Norepinephrine n.s. (vs C2) *Striatum* Dopamine↑, Norepinephrine n.s. (vs C2)
Kim, 2010	Sprague-Dawley (SD) rats (E/C1/C2/C3 = 8/8/8/8)(M/F = 16/0)	3 wk	Neonatal hypoxia-induced hyperactivity model	Not reported	KRG extract 200 mg/kg, p.o., qd, 7 d	C1 neonatal hypoxia + Vehicle, p.o., qd, 7 d C2 control + Vehicle, p.o., qd, 7 d C3 control + KRG extract 200 mg/kg, p.o., qd, 7 d	Open-field test *Total arena* - Total movement distance↓, Total movement duration↓, Rearing frequency↓, Total angle of head bending n.s. (vs C1) *Central arena* - Movement distance↓, Movement duration↓, Rearing frequency↓, Total angle of head bending n.s. (vs C1) Rotarod performance - Falling time↑, Falling frequency↓ (vs C1)	*Forebrain* NET↓ (vs C1)

BDNF, Brain-derived neurotrophic factor; C, Control group; DAT, Dopamine transporter; E, Experimental group; F, Female; KRG, Korean Red Ginseng; M, Male; MDA, Malondialdehyde; n.s., Not significant; NET, Norepinephrine transporter; *p*-TrkB, Phosphorylated tropomyosin receptor kinase B; PCB, Polychlorinated biphenyls; ROS, Reactive oxygen species; WKY, Wistar Kyoto.
Statistical analysis of the outcomes in animal studies showed between-group differences compared to the negative control group.

for sequence generation, performance blinding, random outcome assessment, and sample size calculation, which were not reported [42]. Two other studies did not report several aspects of their methodology but were free of incomplete outcome data and reporting [43,44] (Fig. 3).

3.4. Results of individual studies

3.4.1. Human studies

3.4.1.1. Efficacy. In 1 RCT, 2 g of concentrated KRG extract significantly improved ADHD symptoms in 70 children diagnosed with ADHD based on the DSM-IV criteria, shown by the number of inattention and hyperactivity/impulsivity symptoms and qEEG theta/beta ratio measured at the vertex (Cz) of the children, compared to placebo after 8 weeks of treatment. There was no effect on the salivary cortisol or DHEA levels concerning adrenal function [37].

In an open-label pilot study of 40 children with ADHD, an intervention containing 3 mg of KRG (combination of ginsenoside Rg1, Rb1, and Rg3) and 500 mg of omega-3 (eicosapentaenoic acid, 294 mg; docosahexaenoic acid, 206 mg) was administered for 12 weeks. The primary outcome measures, ADHD-RS, and CGI-Severity scores, showed significant improvements. Attention, memory, and executive function were also improved in neuropsychological tests such as the ATA, auditory verbal learning test (AVLT), Children's Color Trails Test (CCTT), and Stroop Word-Color Test (SWCT) [38]. Subsequently, an RCT was conducted with a larger sample of 120 participants although children with subthreshold ADHD were recruited. This 12-week, double-blind, randomized, placebo-controlled trial showed that the same intervention improved parent-rated ADHD symptoms in ADHD-RS ($p = 0.032$), particularly the inattention score ($p = 0.018$), and emotional and behavioral problems. However, there were no significant improvements in cognitive performance measures (e.g. ATA, AVLT, CCTT, and SWCT) compared to placebo [36].

In a pre-post study, 18 children aged 6–14 years diagnosed with ADHD based on the DSM-IV criteria received 1000 mg of KRG twice daily for 8 weeks; there were significant improvements in omission

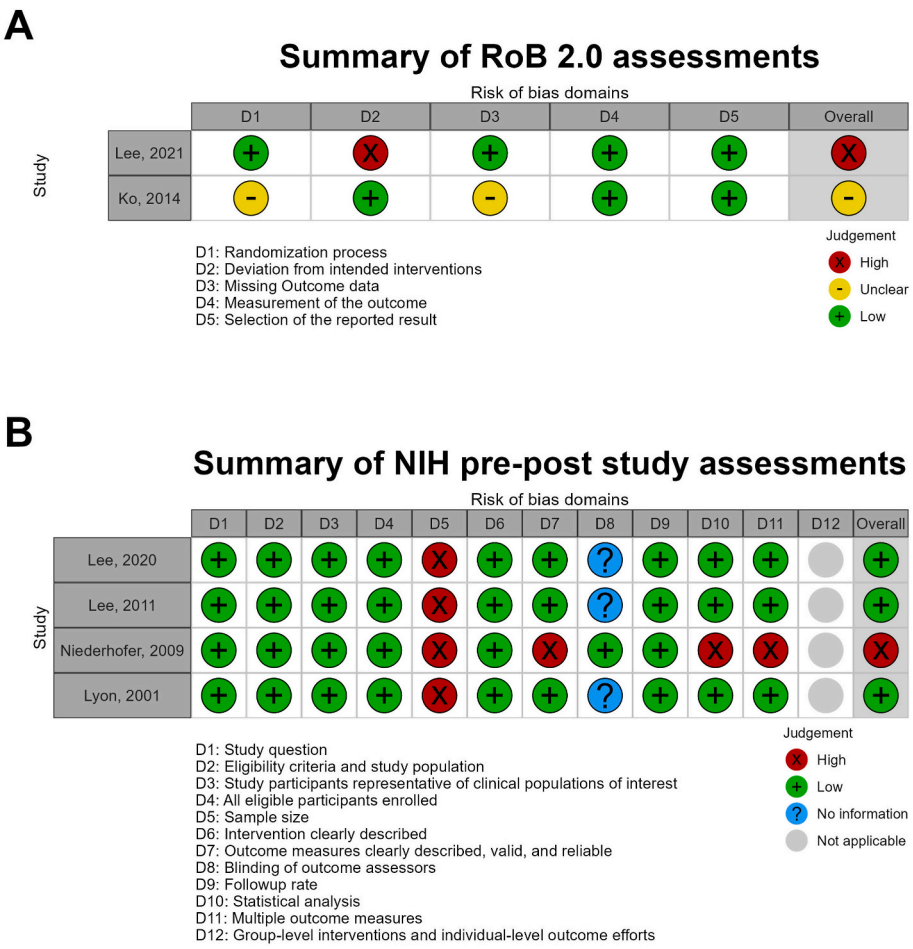

Fig. 2. Quality assessment of human studies included in systematic review of the effects of ginseng and ginsenosides on ADHD. Risk of bias assessment (A) of randomized controlled trials was performed using Cochrane risk of bias assessment 2.0 tool and (B) of pre-post study with no controls was performed using National Institutes of Health quality assessment tool.

errors of ADS, which is a CPT, abbreviated Conners' Parent-Teacher Rating Scale-Revised, and the State Anxiety Inventory for Children (SAIC). This study also found significant reductions in the physical development and social dysfunction scales of the Korean Personality Inventory for Children. However, ADHD-RS, Learning Disorder Scale, CBCL, and Children's Depression Inventory scores did not differ significantly [39].

Considering that Panax ginseng inhibits serotonin and norepinephrine reuptake, one pre-post study evaluated the effect of *P. ginseng* and its constituents on 3 male adolescents with inattention type ADHD. The patients received *P. ginseng* or a placebo for 4 weeks each in a crossover design. The results showed that *P. ginseng* improved both inattention and hyperactivity as examined using ADHD-RS rated by the child, parent, and teacher, and the CGI-Improvement score by a blinded clinician. However, it did not change the omission error but improved the commission error in Conners' CPT. The authors did not present all the results in the control phase and did not perform a relevant statistical analysis [40].

One pre-post test evaluated the effects of an herbal combination containing 200 mg *P. quinquefolius* extract and 50 mg G. *biloba* extract on the symptoms of 36 children with ADHD aged 3–17 years for 4 weeks. Significant improvement from baseline was observed for all the 7 symptom categories and 7 global attributes of Conners' Parent Rating Scale-Revised (long version), which also included DSM-IV criteria scores of ADHD as attributes, after 4 weeks of administration. At least 50 % of the children showed improvement in each of the 3 areas that are most crucial in ADHD (i.e., hyperactivity, cognitive problems, and oppositional behavior) [41].

3.4.1.2. Safety. The intervention reported 1 case of transient headache [38] but an RCT with the same intervention did not report any adverse events [36]. Another RCT on KRG did not report adverse events [37]. One patient complained of mild sedation, which resolved quickly [40]. In a study on *P. quinquefolius*, adverse events included 1 case of being more emotional and impulsive and 1 case of increased hyperactivity and aggressiveness [41], but the authors reported that their ADHD symptoms still improved.

3.4.2. Animal studies

3.4.2.1. Efficacy. In animal studies examining the efficacy of ginseng or ginsenosides, inattention was improved by OAT [42] while hyperactivity/impulsivity and motor coordination were recovered as assessed by OFT [42,44], EPM [42] and rotarod test [44]. All animal studies validated the changes in dopaminergic or norepinephrinergic mechanisms.

One week of oral treatment with red ginseng extract decreased the hyperactivity phenotype of neonatal hypoxia-induced rats. Hyperactivity-related symptoms improved in the OFT and rotarod tests. Red ginseng extract significantly downregulated the expression of NET in the forebrain of hypoxic rats, implying normalization of their catecholaminergic function, which may be linked to their ADHD-like symptoms. The study also performed a Y-maze test for memory/navigation behavior and 5-HT transporters, but there was initially no

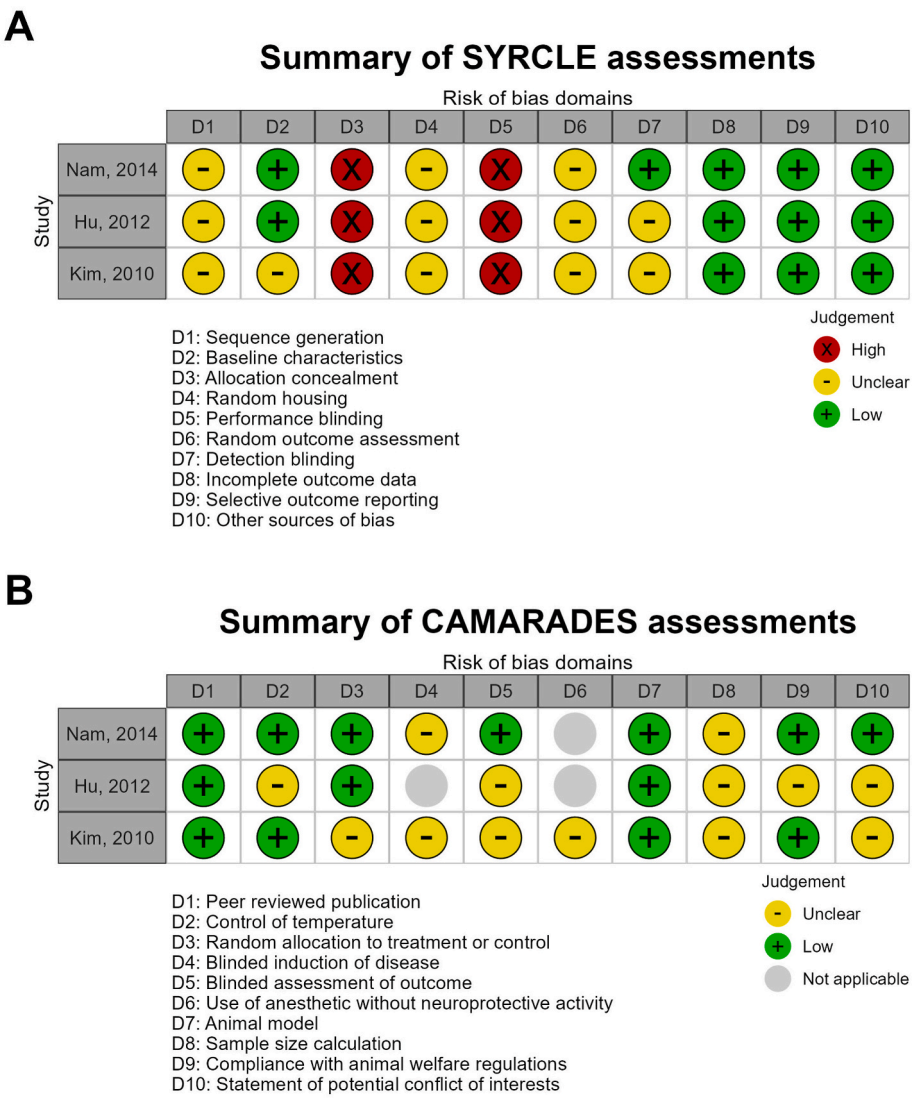

Fig. 3. Quality assessment of animal studies included in systematic review of the effects of ginseng and ginsenosides on ADHD. Risk of bias assessment was performed using (A) SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) and (B) a modified scale from the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES).

significant change in disease induction in the animal model. Interestingly, red ginseng administration in normal rats increased locomotor activity and NET expression in the normal control rats, suggesting a stimulatory effect in normal animals [44].

Ginsenoside Rg1 was investigated to reveal its neurochemical mechanism in treating ADHD using SHR as an animal model. After 14 days of oral administration, dopamine levels were significantly increased, but norepinephrine levels did not show significant changes in the prefrontal cortex and striatum, implying that Rg1 might act mainly on the dopaminergic system [43].

YY162, a mixture of ginsenoside Rg3 and terpenoid-strengthened *G. biloba*, improved ADHD-like conditions induced by PCB in ICR mice. YY162 attenuated the behavioral and biochemical changes, such as attention deficit tested with OAT, and locomotor hyperactivity and impulsivity tested with OFT and EPM. It reversed BDNF/TrkB and DAT/NET signaling and reduced oxidative stress, and its effects, comparable to those of methylphenidate, were mediated by TrkB receptor activation, which was blocked by the TrkB antagonist K252a [42].

4. Discussion

This is the first systematic review to investigate the effects of ginseng and ginsenosides on ADHD. Previous reviews were narrative or systematic reviews which were reviewed with other natural products [45–48]. As ginseng is one of the most popular natural products used for cognitive function and attention, it is necessary to perform a comprehensive review of ADHD [29,30]. This review encompassed 9 studies that examined the effects of Panax species and their components on ADHD in humans and animals and were published between 2001 and 2021 in various countries. Human studies, including 2 RCTs and 4 pre-post studies evaluated the impact of ginseng extract on ADHD symptoms and cognitive function in children and adolescents. Three animal experiments explored the efficacy of ginseng-related compounds in ameliorating ADHD-like behaviors in rat and mouse models using the catecholaminergic system. These results suggest possible benefits in safely reducing ADHD symptoms, particularly inattention but further research is necessary to establish its safety and efficacy.

The efficacy shown in this review should be interpreted cautiously, as it includes more pre-post studies, and only 1 RCT that assessed the efficacy of ginseng alone. The RCTs were more rigorous and reliable than the other designs as they reduced the risk of bias and confounding factors. The pre-post treatment design did not include a control group or placebo, which made it difficult to attribute the changes to the intervention alone. Their underlying mechanisms should be investigated

further from preclinical studies.

Human studies involved children and adolescents diagnosed with ADHD based on the DSM-IV or DSM-5 criteria, and the interventions were KRG extract alone or in combination with other substances. In some studies performed in the 2000s and early 2010s, only male participants were enrolled [39,40] while in others, the proportion of male was 2–3 times higher [37,38]. This could be a confounding factor for the results as hyperactivity is more distinct in boys and diminishes at a younger age, while inattention is more frequent in females and generally persists till adolescents [49,50].

The outcome measures in human studies varied from ADHD symptom scores to neuropsychological tests and neurochemical levels. Every study used ADHD symptom scores according to DSM criteria; 1 study used simple counting of ADHD symptoms [37], another study used the DSM-IV symptoms subscale in the Conners' ADHD Rating Scale [41], and the remaining used ADHD-RS [36,38–40] as the primary outcome. Most studies showed that ginseng or ginseng-containing products have beneficial effects on ADHD symptoms, especially inattention, which improved in 1 RCT and 2 pre-post studies [36,39,40], while 1 RCT and 1 pre-post study reported improvements in both inattention and hyperactivity [37,38]. As some studies enrolled patients with inattentive type of ADHD or higher scores of inattention at baseline, the results may show better improvement in inattention scores due to the floor effect of hyperactivity [36–38,40].

The results of CPT are equivocal to those of the ADHD symptom scales. Computerized CPT (e.g. ATA, ADS, and Conners' CPT) have also been used in most human studies [36,38–40]. Within-group differences in CPT parameters were statistically different in both the RCT and pre-post studies, but between-group differences were not significant in 1 RCT [36,38–40]. Within-group differences in commission errors, which are related to impulsivity and disinhibition [36,38,40] and response time, which is related to inattentiveness [36,38] improved, while omission errors, which are related to selective attention, improved only in 1 study [39]. A significant pre-post difference in response variability, which was related to inconsistency and sustained attention, was reported in 1 study [39,51]. Although CPT tests cannot replace subjective psychiatric interviews, observations, and other clinical assessments for diagnosis [52], the results should be considered for its effect.

Animal studies used rat or mouse models induced to exhibit ADHD-like behavior and examined the effects of ginseng and ginseng-related compounds on behavior and the underlying neurochemical changes. The included animal studies used 3 different models of ADHD: PCB-exposed [42], SHR [43] and neonatal hypoxia-induced hyperactivity models [44]. There are two categories of ADHD models which are genetic and non-genetic models. The currently available models mainly feature hyperactivity, but do not fully reflect other behavioral phenotypes of ADHD [53]. SHR, a frequently used genetic model, exhibits hyperactivity, impulsivity, inattention, and working memory deficits due to altered dopamine and norepinephrine systems in the fronto-striatal system but there is some concern that its original hypertensive basis may not be directly related to ADHD [54,55]. The neonatal hypoxia model features hyperactivity and learning deficits due to alterations in the dopaminergic, norepinephrinergic, and serotonergic systems. However, hypoxic damage does not accurately mimic the clinical presentation [56]. The PCB-exposed model is impulsive and hyperactive but does not show sustained attention [53]. Since the human studies showed efficacy in inattention, the discrepancies between human and animal studies might be due to this limitation.

The included studies investigated changes in the prefrontal cortex [42–44] and striatum [43], which are critical regions in the dopaminergic pathway. Dopamine was significantly altered by both ginsenoside Rg1 alone and ginsenoside Rg3 with *G. biloba* [42,43]. Rg1 is reported to upregulate vesicular dopamine content and increased exocytosis frequency while modulating dopamine release during exocytosis in PC12 cells, suggesting a potential nootropic role [57]. Norepinephrine, another major target for ADHD treatment, was also investigated in animal studies. NET changed when red ginseng extract was introduced into neonatal hypoxia-induced rats [44]. However, Rg1 alone did not change norepinephrine in either the prefrontal cortex or striatum, while ginsenoside mixed with a non-ginseng compound changed NET expression [42,43]. Norepinephrine-related effects may differ based on the types of ginsenosides. Although the included studies in this review mainly focused on Rg1 as a single compound, other compounds such as ginsenoside Rb1, Rd, and Re could also be potential candidates for ADHD treatment. Rb1, Rd, and Re have been shown to increase norepinephrine in the frontal cortex and increased dopamine in the hippocampus and striatum of mice under the chronic unpredictable mild stress test [58]. Among them, Re dose-dependently increased dopamine and acetylcholine release in the medial prefrontal cortex and hippocampus of freely moving rats, which may contribute to learning and memory [59]. Rd has a protective mechanism against LPS-induced neuroinflammation in dopaminergic neurons, which could be relevant for conditions involving altered dopamine neurotransmission [60]. It was found that Rb1 modulated both dopamine and norepinephrine levels in the frontal cortex of mice in response to immobilization stress [61]. The effect of ginseng and ginsenosides on dopamine and norepinephrine modulation has been reported in many studies. Ginsenosides of *P. ginseng* simultaneously increased dopamine levels and norepinephrine levels in brain including cerebral cortex under various conditions such as normal diet, protein deficiency, hypobaric and hypoxic environments [62–64]. Additionally, in chronic mild stress model of depression, ginsenosides increased both dopamine and norepinephrine in hippocampus [65,66]. Especially, dopamine has been extensively studied in vitro and in vivo models of Parkinson's disease. These models have demonstrated that KRG [67–69], *P. ginseng* [70,71], Rg1 [72–75], Rb1 [75,76], Re [76], and panaxatriol ginsenosides [77] regulated dopamine-related markers. Further screening should be conducted in the future to differentiate the ginsenosides that control the dopaminergic and norepinephrinergic pathways in ADHD-relevant models, as most studies investigating these pathways were performed in models of different diseases.

The reported adverse events were mild and transient and no serious side effects were observed. Comprehensive safety data is crucial since juvenile brain development is a critical period. The utilization of ginseng in pediatric populations varies globally. In countries such as Korea, China and Japan, ginseng is commonly incorporated into pediatric treatments, supported by a substantial number of randomized controlled trials (RCTs) and endorsed within clinical practice guidelines on diverse pediatric disorders including ADHD and autism spectrum disorder [78–83]. In Korea, children are one of the biggest population who consume ginseng [84]. In contrast, the European Medicines Agency advises against its use in those under 18 due to insufficient research [85]. This discrepancy highlights the debate over pediatric use of ginseng. Nevertheless, RCTs included in this study offer evidence supporting its use in children. Other ginseng studies conducted in children indicate a low risk of adverse events, although studies on this population are scarce. For instance, children with leukemia and solid cancers did not experience adverse events after receiving 60 mg/kg daily of KRG for a period of one year, showing a stabilizing effect on inflammatory cytokines [86]. Similarly, *P. quinquefolius* did not cause significant serious adverse events in children with upper respiratory infections [87]. Given the prolonged usage in the previous RCTs and the included studies of this systematic review, use of ginseng in children may be taken into consideration.

The appropriate dosage of ginseng or ginsenosides for ADHD is also a matter of concern. While the human studies included in this study used 1,000 mg of KRG [37,39] or 250 mg of panax ginseng [40] when used alone, the human equivalent dose (HED) can be calculated from the animal studies. Direct references for calculating the HED specifically from neonatal animal data to humans, including pediatrics, are not commonly found in standard guidelines, unlike those for adult animal to adult human conversions. In the absence of such data, use of KRG in

pediatric populations should be guided by careful consideration of the available adult data, adjusted for children's unique metabolic and physiological profiles using general pharmacokinetic principles and scaling methods. A dose of 200 mg/kg of KRG extract was administered to 3-week-old Sprague-Dawley (SD) rats in the study by Kim et al. [44]. As the weight of the experimental animals was not provided by the author, the average weight of the animals was obtained from other sources. Specifically, the average weight of 3-week-old male SD rats was found to be 54g, while that of 8-week-old male SD rats was 311g [88]. Based on body weight$^{3/4}$ allometric scaling, the converted dose for 8-week-old SD rats was 743.54 mg/kg [89]. Using the correction factor ratio (*Km*) between humans and rats, the converted human equivalent dose (HED) from the animal dose for a 60 kg adult was 140.67 mg/kg [90]. As body weight is the most important factor for clearance after 2 years old to calculate the dose for a child, the dose was extrapolated using body weight allometric scaling with the formula body weight$^{3/4}$ [91,92]. The average body weight of a 10-year-old child is 31.5 kg [93], resulting in an HED of 86.76 mg/kg, which is approximately 2732.95 mg. Similarly, the human equivalent dose (HED) of ginsenoside Rg1 in 10-year-old children can be estimated as 4.67 mg/kg, approximately 147.02 mg [43]. The doses used in RCTs and pre-post studies were about 2.7 times lower than the HEDs from animal studies. The doses used in the previous clinical studies varied in the range of 0.9g–60g of red ginseng extract and powder to adults [94]. In the National Herbal Medicine Information (NHMI) database, it is indicated that *P. ginseng* can be administered in a daily dose of 2–30g [95]. As a dietary supplement, the recommended dose of KRG is a daily intake of 3 mg–80 mg of the combined total of ginsenosides Rg1, Rb1, and Rg3 and can be used for memory improvement [96]. Currently, pharmacokinetic studies on ginseng and ginsenosides have mainly focused on adults, with limited research specifically delineating age groups that would highlight pediatric populations [97,98]. To ensure precise and safe use in children, further targeted research is necessary to establish specific dosing guidelines and pharmacokinetics in pediatric populations. In addition, it is worth noting that calculating the dose based on mg/kg has not been found to be helpful in treating ADHD, as variations in dose are not related to height or weight [99]. Therefore, further investigation is required to determine the appropriate dose for ADHD.

The duration of sustained cognitive effects following the cessation of ginseng administration is also crucial in determining the appropriate frequency of its use. The relevant data on cognition were only found in the study on the Alzheimer's disease population, although the results cannot be directly adopted. One study reported that the cognitive functions of patients with Alzheimer's disease improved and were maintained with both 4.5 g/day and 9.0 g/day of red ginseng supplements during 2 years of follow-up [100]. However, in another study, the benefits of ginseng compared to the control treatment were not maintained after a 12-week washout period [101]. These equivocal results raise the question of whether ginseng serves as a transient cognitive stimulant or enhancer.The results of human and animal studies suggest that ginseng and its components may be effective in alleviating ADHD symptoms, particularly inattention. One of the main differences in the definition of ADHD between DSM-IV and DSM-5 is that the subtypes of ADHD have been replaced with presentations in that symptoms can change with age [49]. Some included studies only considered children with inattention-type ADHD. However, because hyperactivity tends to wane with age but inattention persists [49], our finding that ginseng is more effective in reducing inattention indicates its clinical importance in older patients with ADHD. At present, in the majority of clinical practice guidelines in nations, methylphenidate is recommended the first-line treatment for both children and adolescent ADHD and adult ADHD [102–106]. According to the network meta-analysis of RCTs, methylphenidate demonstrated the most favorable benefit-to-risk ratios for children and adolescents, while amphetamines exhibited the most favorable benefit-to-risk ratios for adults in the short-term treatment of ADHD, with consideration of side effects [107]. Given the target of both medications, the results from ginseng may be applicable to adults with ADHD. Memory, one of the important profiles in ADHD, showed within-group differences but not between-group differences, although it was examined in a few studies which used an extremely low dose [36,38]. There is evidence that memory is improved in healthy adults or in animal studies of dementia, so the memory-enhancing effects of ginseng and ginsenosides at an appropriate dose should be validated further [15,29,108]. Ginseng is a promising agent for the treatment of neurodegenerative diseases, particularly Alzheimer's disease. Ginsenosides, such as Rg1 and Rg3 have demonstrated neuroprotective properties and the ability to improve learning and memory capabilities in animal models with memory impairment [15,109–111]. Additionally, the effects of ginseng and its constituents on brain and the nervous system have been explored [112,113]. Ginsenosides exert anti-inflammatory and autophagy-promoting activities, which could be beneficial in aging-related neuroinflammatory conditions [114].

Another strategy involves the use of ginseng in combination to improve its efficacy. The combination of ginseng and omega-3 or *G. biloba* improved ADHD-RS inattention score [36]. *P. quinquefolius* improved ADHD symptoms with reduced dose of *G. biloba* from 240 mg/d to 100 mg/d [41,47].

The limitations of this study were as follows. Most studies were pre-post studies and did not include comparisons with control groups. Although some studies blinded the assessors, they still had a somewhat high risk of bias owing to incomplete blinding and placebo effect. Some studies used a mixture of other compounds such as *G. biloba* and omega-3. Although studies on ginseng alone and in combination with other ingredients showed significant benefits for ADHD, the limitation of having only a small number of studies included in this review underscores the need for further research. Specifically, randomized controlled trials (RCTs) with larger sample sizes are essential to validate the efficacy. Moreover, the existing studies lacks detailed information to confirm optimal dosage and treatment duration. The variation in the types of ginsenosides used across different studies suggests that the specific active ingredients contributing to the observed effects are still unclear. Identifying these components is crucial for enhancing the generalizability of findings and developing more effective ADHD treatments. Further, the effects of other species of the genus Panax should be investigated with a control group, because the only study that evaluated the efficacy of *P. quinquefolius* assessed it in combination with *G. biloba* [41]. As 1 of the 2 included RCTs recruited only patients with subthreshold ADHD, the validity of the genuine effect of ginseng is limited and further well-designed RCTs are necessary. Five of the 9 studies were written by Korean authors, and there is a risk of publication bias so the results may be skewed. The included studies tested the effects only in children or adolescents, although adult ADHD has been rapidly increasing since the 2020s. However, previous studies have shown the promising effects of ginseng on cognition in healthy young adults [29,30].

5. Conclusions

This comprehensive systematic review highlights the potential therapeutic roles of ginseng and its ginsenosides in the treatment of ADHD. The included studies, comprising both human and animal experiments, indicated their potential efficacy in improving ADHD symptoms, particularly inattention, without any noticeable adverse events. Ginseng and its constituents may alleviate symptoms by modulating catecholaminergic neurotransmitter pathways, including dopamine and norepinephrine, and influencing neurotrophic signaling pathways, such as BDNF/TrkB. Investigating various ginsenosides or several species of the Panax genus and exploring combination therapies may provide valuable insights into their potential therapeutic benefits. However, owing to the limited number of RCTs and variations in study quality among different types of studies, further rigorous study designs and reporting are necessary to establish the safety and efficacy of

ginseng for ADHD. Continued research could lead to alternative and integrative approaches for addressing ADHD-related challenges and reducing the limitations of currently available treatments.

Declaration of generative AI in scientific writing

None.

Data statement

No new data were created or analysed in this study. Data sharing is not applicable to this article.

Authorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *Journal of Ginseng Research*.

Declaration of competing interest

There are no conflicts of interest to declare.

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Appendix A. Supplementary data

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