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Review Article

Iranian Traditional Medicine for Treatment of Attention Deficit Disorder with Hyperactivity in Children: A Systematic Review of Randomized Controlled Trials

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with a complex etiology. Stimulants as a first-line treatment are not effective in some cases. In this study, we conducted a systematic review to evaluate the efficacy of traditional Persian Iranian medicine (TIM) for children and adolescents with ADHD.

Methods: Data were collected mainly from PubMed, Google Scholar, Web of Science, ProQuest, and Scopus databases until Dec 2022. The keywords related to ADHD, traditional Persian medicine (TPM), and (TIM) were searched. Two reviewers independently screened 714 abstracts and eventually, eight trials were included in the systematic reviews. Changes in the severity of ADHD symptoms were considered based on the validated cutoff on recognized rating scales as the result of the effect of TIM on ADHD.

Results: Interventions included herbal extracts of *Passiflora incarnate*, whey protein, *Ginkgo biloba, Crocus sativus L*, sweet almond syrup, and horse milk. In all studies, except *G. biloba*, there was evidence of a reduction in the severity of ADHD. Low evidence could be found for *G. biloba*.

Conclusion: Herbal and traditional remedies are an efficient and safe solution to alleviate the symptoms of ADHD. In future studies, TIM as a complementary therapy may be useful to alleviate ADHD symptoms, especially in children who are resistant to stimulant medications.

Keywords: Hyperactivity; Traditional Persian medicine; Traditional medicine; Complementary and alternative medicine

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children and adolescents. The worldwide prevalence of ADHD was 3%-5% (1, 2). The disorder shows phenotypic heterogeneity characterized by patterns of inattention and/or hyperactivity/ impulsivity (3). The male/female ratio of ADHD is 2-9:1 (4). A combination of genetic and environmental factors affects the occurrence of ADHD, but the exact cause has not yet been established (5).

There are multiple approaches to the treatment of ADHD, but pharmacotherapy with stimulants (such as methylphenidate (MPH) and atomoxetine) are the first-line medications (6). MPH is the most commonly used stimulant in Iran. MPH inhibits the reuptake of both dopamine and noradrenaline and increases dopaminergic and noradrenergic activity in the prefrontal cortex. Dysregulation of these neurotransmitters is central to the pathophysiology of ADHD (7). Although, MPH has been considered an effective drug, insomnia, nausea, and loss of appetite, have been reported as common side effects of MPH (8). In addition, the evidence reported that about 25% - 30% of children with ADHD do not respond to MPH (9). Treatment failure and the occurrence of side effects of stimulants in some patients may lead families to seek complementary and alternative medicine (CAM) such as herbal remedies, dietary supplements, neurofeedback, and homeopathic therapy. Current evidence suggests that 12%-64% of children with ADHD use some form of CAM (10, 11).

Traditional medicine has existed in Iran, Egypt, India, Japan, China, and other parts of the world for thousands of years. The Medieval medicine in Iran, by people like Hanin Ibn Ishaq, Mohammad Zakaria Razi, Haly Abbas, and Ibn Sina (Avicenna) has played a vital role in the development of traditional medicine in the world (12, 13). Considering the expansion of the use of CAM throughout the world and the strong historical and cultural support in this field, the use of TIM along with modern medicine integration may be a good solution to promote community health and the treatment of diseases (14).

Temperament is the key concept in TIM and diagnosis of the disease is made by considering the temperament of the organs and the patient's temperament, season, mental state examination, etc. (15, 16).

Although there was no specialized term for ADHD in ancient TIM literature. However, there are signs of disorders associated with ADHD in ancient Iranian texts such as the Canon of Medicine (Ibn Sina) despite the lack of a specialized definition of ADHD in ancient literature; in texts such as the Canon of Medicine (Ibn Sina), there are some definitions of symptoms related to ADHD (17).

According to traditional medicine, two factors, heat, and dryness, increase extreme activity or hyperactivity in children. Bile and soda are the leading causes of this disorder, which if left untreated can cause many mental and physical complications in the child, such as blurred vision, baldness, constipation, aggression, anger, physical fights, depression, and despair.

Among the treatments for hyperactivity in traditional medicine are bile and soda abstinence and related measures, monthly cupping, consumption of honey vinegar, and consumption of herbal remedies (17).

Herbal and traditional remedies are more acceptable for some people in Iran and sometimes patients or their parents use CAM in combination with modern medicine without noticing drug interaction and their side effects.

A meta-analysis study conducted in 2022 reviewed the effect of East Asian herbal medicine (EAHM) on ADHD severity. EAHM has been used to treat mental illnesses in children for a long time and is safe, they concluded that monotherapy with EAHM is effective and has fewer side effects than stimulant medications (18).

In another meta-analysis study that examined the effects of various medicinal plants on this disorder, they found evidence of the positive and safe effects of plants such as *Melissa officinalis* L., *Bacopa Monnieri* (L.) Wettst., *Matricaria chamomilla* L., and *Valeriana officinalis* L (19).

Therefore, we aimed to provide a comprehensive overview of the scientific evidence regarding the efficacy and safety of TIM for the treatment of ADHD.

Methods

This systematic review was consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study was registered at PROSPERO (ID: CRD42022340892).

Search strategy

We searched the following electronic databases: PubMed, Google Scholar, Web of Science, ProQuest, and Scopus. The database at any date until December 2022 was searched. Moreover, a manual search was done to identify gray literature and eligible studies.

Inclusion and exclusion criteria

Inclusion criteria

Studies were eligible to be included in this systematic review if they met the following criteria:

1. Randomized controlled trials (RCT)
2. Full-text articles in English or Persian language
3. Conducted on children and adolescents between 0 and 18 years of age who showed symptoms of ADHD
4. Diagnosis of ADHD based on DSM-IV or Diagnostic and Statistical Manual of Mental Disorders and different standardized instruments for measurement with no restrictions on participant sex, and comorbidity
5. Involved administration of mono or compound herbal preparations of any form, dose, and duration plus standard conventional treatment or versus standard conventional treatment

Exclusion criteria

1. had insufficient information
2. Reported in languages other than English or Persian
3. Incomplete articles or obscure statistical results

Data selection and extraction

Two reviewers independently screened the citations retrieved during the search and full-text publications. Any differences were resolved through discussions with a third reviewer. The authors extracted data from eligible studies and recorded the authors, publication years, sample size, outcome measures, herbal intervention type, and treatment duration.

Quality assessment

The risk of bias assessment is presented in Table 1. This evaluation was done using the Cochrane collaboration tool. This tool is used to assess the biases of clinical trials in review studies and has five domains, which include bias arising from the randomization phase, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the outcome measurement and bias in the selection of the result (20).

Table 1: Summary of risk of bias according to the Cochrane Collaboration

Author (Reference)	*Random sequence generation*	*Allocation concealment*	*Blinding of participants and personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*	*Other sources of bias*
Zeinab Mostajearn et al., 2020 (22)	+	+/-	?	-	+	?	+/-
Monireh Sadat Motaharifard 2019 (27)	+	?	?	-	+	+	+/-
Sara Baziar 2019 (26)	+	?	?	-	+	+	+
Fereshteh Shakibaei 2015 (24)	+	?	?	-	+	+	?
Bahman Salehi 2010 (23)	+	?	?	-	?	?	+
Shahin Akhondzadeh 2005 (21)	+	?	?	-	+	+	?
Mojtaba Khaksarian et al., 2021 (25)	+	+	+	-	+	?	?
Jokar et al., 2022 (28)	+	+	+	-	+	?	?

Results

Search results

Details of the search data are presented in Fig. 1. A total of 714 pieces of literature were obtained through the literature search, out of which 444 were selected after the removal of duplicate studies. Four hundred and twenty articles were excluded after reading the title and abstract. twenty-four full texts were examined for eligibility, and a further 12 articles were excluded since these were not RCTs, did not provide relevant data, and were not original. Six studies were considered for general review. Details of the search data are presented in Fig. 1. We included eight studies in the systematic review.

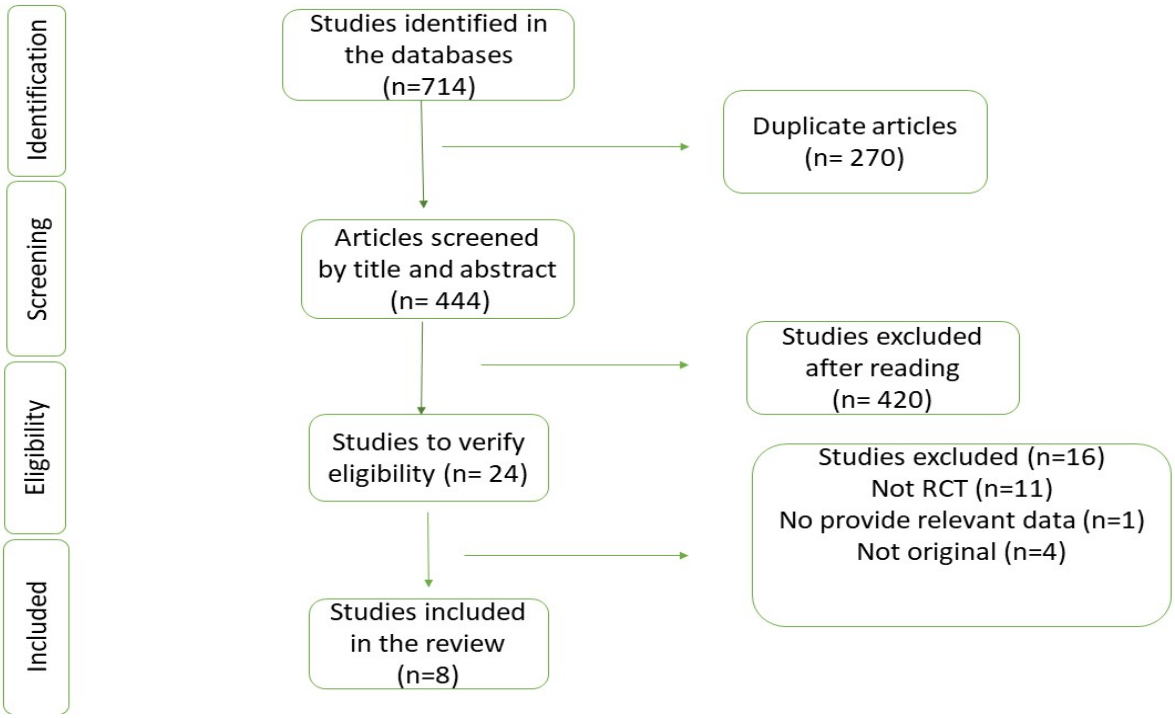

Fig. 1: Flow of Trials through the Systematic Review.

Characteristics of included articles

The characteristics of the included articles are shown in Table 2. All of the studies were conducted in Iran and were randomized trials. The total number of participants was 412. The sample size ranged from 30 to 70 individuals. In all studies, subjects under the age of 18 were diagnosed with ADHD based on the DSM. Three trials compared TIM with MPH and five trials compared TIM/MPH with MPH. The duration of intervention in the studies was between 6 and 8 wk.

Results

Table 2 summarizes the study characteristics. The most important findings of these selected studies were as follows.

Table 2: Characterized and extracted data of the included studies

Author and year of publication	*Subjects*	*Intervention*	*Outcome measures*	*Results and level of significance*
Zeinab Mostajearn et al., 2020 (22)	64 children with ADHD	Whey protein(ma'aljobon) 25 g once daily plus standard conventional treatment (SCT) or control group (SCT only)	Scores of the Strengths and Difficulties Questionnaire (SDQ) and Conner's' Continuous Performance Test (CPT)	Hyperactivity scale of SDQ showed a significant decrease in the intervention group compared to the control group (p = 0.04). there was a significant improvement in the intervention group regarding attention and focus score based on CPT (p = 0.01)
Monireh Sadat Motaharifard et al., 2019 (27)	) children with ADHD	Methylphenidate (10 mg) or sweet almond syrup 5 cc/day (three times a day)	Parent and Teacher ADHD Rating Scale	Two treatments had similar effects on symptom reduction in ADHD children. No significant differences were observed between the two groups (p=0.13 and p=0.47).
Sara Baziar et al., 2019 (26)	0 children with ADHD	20–30 mg/d (20 mg/d for <30 kg and 30 mg/d for >30 kg) MPH or 20–30 mg/d saffron capsules depending on weight (20 mg/d for <30 kg and 30 mg/d for >30 kg).	Teacher and Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV)	No significant difference between the two groups on Parent and Teacher Rating Scale scores (p = 0.425, and p = 0.701, respectively). Changes in Teacher and Parent ADHD Rating Scale scores were not significantly different between the saffron group and the MPH group (p = 0.731 and p = 0.883, respectively).
Fereshteh Shakibaei et al., 2015 (24)	60 Children with ADHD	methylphenidate (20e30 mg/day) plus either G. biloba (80-120 mg/day) or placebo	Parent and teacher forms of the ADHD Rating Scale-IV (ADHD-RS-IV)	More reduction was observed with G. biloba regarding ADHD-RS-IV parent rating inattention score (P < 0.001) and total score (P < 0.001) as well as teacher rating inattention score (P = 0.004). The response rate was higher with G. biloba compared with placebo based on parent rating (P = 0.002).
Bahman Salehi et al.,2010 (23)	50 children with ADHD	80–120 mg/day depending on weight or methylphenidate at a dose of 20–30 mg/day depending on weight	Parent and Teacher Rating Scale scores.	Significant differences were observed between the two groups on the Parent and Teacher Rating Scale scores. (p= 0.002 for Parent ADHD Rating Scale (inattentive) p= 0.0001 for the Teacher ADHD Rating Scale (inattentive) p= 0.003 for Parent ADHD Rating

Table 2: Continued…

				Scale (hyperactive/impulsive) and p= 0.0001 for Teacher ADHD Rating Scale (hyperactive/impulsive)
Shahin Akhondzadeh et al., 2005 (21)	34 children with ADHD	Group 1 received *P. incarnata* L. 0.04 mg/kg/day (twice daily) and group 2 received MPH 1 mg/kg/day (twice daily)	Parent and Teacher Rating scales.	No significant differences were observed between *P. incarnata* L. and methylphenidate on the Parent and Teacher Rating Scale scores throughout the trial (p = 0.93; and p = 0.94, respectively). Both treatment groups demonstrated Significant clinical benefit for treatment as assessed by both parents and teachers.
Mojtaba Khaksarian et al., 2021 (25)	70 children with ADHD	Both groups received 20 or 30 mg/d of MPH (20 and 30 mg/d for < 30 and > 30, respectively), and one of them also received 20 or 30 mg/d of saffron in a capsule based on BMI (20 and 30 mg/d for < 30 and > 30, respectively).	DHD-RS-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV)	Efficacy of the combination of MPH and *C. sativus* (saffron) over MPH alone in the treatment of patients suffering from ADHD. (P < 0.05).
Jokar et al., 2022 (28)	30 children with ADHD	250 ml cow milk or horse milk plus MPH (1mg/kg/day)	Conners rating scale (CS)	CS of the parents decreased significantly (P ≤0.001) in the group that first received horse milk. After consumption of horse milk, the parent's CS was significantly different from that of cow milk (P = 0.001). Teachers' CS decreased significantly following horse milk consumption (P=0.001)

P. incarnate L. had similar effects compared to methylphenidate and at the end of the study, no significant differences were observed between *Passiflora* and MPH on the Parent and Teacher Rating Scale scores (21). In the study of Mostajeran et al. (22), *ma'aljobon* combined with standard conventional treatment (SCT) caused a better reduction in the hyperactivity score of ADHD children compared to SCT based on the Strengths and Difficulties Questionnaire (SDQ). However, no significant differences were observed in other scales of SDQ between groups. In addition, there was a significant improvement in the attention and focus scores in the interven-

tion group based on the Continuous Performance Test. Two included studies examined the effects of *G. biloba* in children with ADHD in Iran. In the first study, children with ADHD were treated with *G. biloba* (group 1) or MPH (group 2) for 6 wk. The difference between the two groups in terms of Parent total score and Teacher Rating Scale scores (total score) was different in the two groups. In group 2, there was more improvement than in group 1 (23). In another study, children and adolescents with ADHD were treated with MPH and *G. Biloba* or MPH for 6 wk. A better recovery was found in parent rating inattention score, total score, and teacher rating inattention score in the intervention group (24).

In another study, 6 weeks of treatment with MPH or saffron (*C. sativus)* showed no significant difference in parent rating scale score, and the two groups showed similar improvement (25).

It has been observed in a study that a combination of saffron and MPH is more effective in treating patients with ADHD than using these treatments separately. Prescribing this combined treatment can enhance its effectiveness and reduce the duration of therapy (26).

Children with ADHD received MPH or sweet almond syrup. Two treatments had similar effects on ADHD symptoms. No significant differences were observed between the two groups (27).

In a 2022 study conducted by Jokar and colleagues, horse milk was compared to cow milk as a treatment for ADHD symptoms in 30 children and the results showed that horse milk consumption of horse milk was significantly more effective than cow milk in reducing the severity of symptoms (28).

Discussion

Dysfunction of synaptic transmission like neurotransmitter disorders (dopamine, norepinephrine, serotonin, etc.) plays a pivotal role in the pathophysiology of ADHD (29, 30). Herbal remedies may have a beneficial effect on the neurotransmitter system, which is explained in detail for each selected study below.

In this review, 8 articles were selected, which include, herbal extracts of *P. incarnata*, whey protein*, C. sativus, G. biloba*, and sweet almond and horse milk. In all studies, except *G. biloba*, there was evidence of a reduction in the severity of ADHD**.**

P. incarnata L. is known as an herbal medicine that has sedative/anxiolytic properties used for stress, anxiety, insomnia, and hysteria (31). The British Herbal Compendium approved the use of *P. incarnata* for ADHD symptoms (32). Supplementation with *P. incarnata* (100 mg/kg/day) significantly increased dopamine and affected the mRNA expression of the synthetic and metabolic enzymes in neurotransmitter pathways such as monoamine oxidase (MAO), catechol-O-methyl transferase (COMT), and glutamic acid decarboxylase (GAD) in mice (31). The effect of *P. incarnata* (500 mg/kg/day for 5 consecutive days) led to increased gamma-aminobutyric acidergic (GABAergic) neuron activity, blood melatonin, and serotonin (5-HTT) levels in mice (33). Some of the studies have shown decreased levels of 5-HTT in the blood of children with ADHD compared with healthy controls (34). Blood serotonin levels appear to be inversely related to brain serotonin levels (34). Probably increasing the level of serotonin in the blood by consuming *P. incarnata* correlates with reducing the level of serotonin in the brain and a decrease in 5-HTT activity in various brain regions may be associated with reducing some symptoms of ADHD.

GABA is the main inhibitory neurotransmitter of the central nervous system (CNS) that regulates sleep and melatonin is synthesized from serotonin in the pineal gland and used as a sleep regulator and circadian rhythm (35). One of the side effects of stimulants such as MPH is insomnia and other sleep problems (8), increased GABA and melatonin because of consuming *P. incarnata* could be effective in improving sleep disturbance in children with ADHD. *P. incarnata* can increase the duration of sleep and decrease wakefulness, and the justification for this was that this is pos-

sible by binding to the GABA-site of the GABAA receptor (36).

Whey Protein is known as *Ma'aljobon* in TIM (37). Whey proteins have bioactive properties (lactoferrin, beta-lactoglobulin α-lactalbumin, glycomacropeptide) which make them an antioxidant, antihypertensive, antitumor, hypolipidemic, antibacterial, antiviral, and chelating agent (38).

α-lactalbumin as one of the main components of Whey Protein has a high content of tryptophan level as a precursor of serotonin. Elevated serum tryptophan levels can lead to crossing this amino acid from the blood-brain barrier in competition with other large neutral amino acids and may increase brain serotonergic activity (39, 40).

Anxiety is one of the most common problems in ADHD children that is related to reductions of 5-HT in the forebrain (41). A relative increase of serotonin in the brain can reduce anxiety symptoms and thus help improve the symptoms of ADHD, of course, there is a conflicting hypothesis that relieving anxiety in children with ADHD can reveal the symptoms of ADHD that was masked by the anxiety (42). Comorbidity of tics, depression, and obsessions is also seen in these children (43). Increasing the activity of serotonin in the brain can help in the treatment of obsessions and depression (44, 45), and on the other hand, reducing anxiety, can be effective in treating tics (46). Despite a sharp increase in serotonin; as mentioned above, is associated with an increase in the symptoms of ADHD. With this description, the regulation of serotonin levels in ADHD is a double-edged sword that should be done by a child and adolescent psychiatrist with close monitoring.

Whey protein is also able to decrease the inflammation markers such as TNFα, IL1β, and IL6 (47, 48). Cytokine-mediated inflammation is an important pathogenic factor in ADHD correlated with the severity of symptoms (49). Inflammatory cytokines could change the neural pathways of the developing brain, attention, and memory with their effect on neurogenesis and synaptic plasticity in some regions of the brain (50, 51).

G. biloba is considered another medicine that could increase the level of dopamine and\ acetylcholine levels in the rat medial prefrontal cortex and improve cognitive function, memory, and motivation (52, 53). Treatment with *G. biloba* (100 mg/kg) for 14 d could increase extracellular dopamine and noradrenaline levels in rats. A possible hypothesis for the effects of *G. Biloba* could be the down-regulation or desensitization of receptors modulating dopamine and noradrenaline release in the mesocortical and mesolimbic pathways (53).

The dopamine hypothesis of ADHD is one of the most important ideas in this field, and the treatment with stimulants is in this direction in such a way that they are blocking the dopamine re-uptake mechanism in the striatum, which leads to a reduction in the symptoms of ADHD (54).

Increasing the function of acetylcholine may lead to improved cognition and thus could be beneficial in the improvement of attention in ADHD (55, 56). New medical approaches have been proposed for ADHD that target the nicotinic acetylcholine receptor (nAChR) and have a beneficial effect on the cognitive and emotional domain, then this remedy may be beneficial in reducing symptoms of ADHD due to dopaminergic and cholinergic effects (57, 58).

G. biloba can also have antioxidant properties, scavenging various reactive oxygen species, including superoxide, peroxide, and hydroxyl radicals. *G. biloba* has been reported to enhance the activities of superoxide dismutase, and catalase, and decrease lipid peroxidation in the striatum, substantia nigra, and hippocampus (59, 60). Increased oxidative stress and disturbance of the ratio of antioxidants to oxidative status have been studied in various studies on ADHD (61-63). Animal models of ADHD show acute administration of high doses of MPH can lead to increases in DNA damage, oxidative and inflammatory changes in brain cells, and induce neurodegeneration in the hippocampus and cerebral cortex (64, 65). The prescription of *G. biloba* may have a compensation effect in this matter.

C. sativus also known as saffron could improve memory and has antidepressant, antianxiety, and neuroprotection properties (66). It can increase the reuptake inhibition of dopamine and norepi-

nephrine. *C. sativus* (50, 100, 150, and 250 mg/kg, i.e.) increased brain dopamine concentration in a dose-dependent manner. The dose of 250 mg/kg increased the production of dopamine and glutamate in rat brains (67).

In addition, it can also be considered as an antagonist N-methyl D-aspartic acid (NMDA) receptor that could normalize the glutamatergic system and ameliorate cognitive and memory deficits. *C. sativus* is also known as a GABA agonist that could improve the sleep patterns of these children (68- 70).

Sweet almond has long been used in TIM (71). It has a high content of vitamin E and unsaturated fatty acids. It can be considered an antioxidant and anti-inflammatory substance and it seems to have neuroprotective properties (72). Long-term intake of sweet almonds significantly elevates whole-brain serotonin levels, the improvement of ADHD symptoms (73).

On the other hand, the antioxidant and anti-inflammatory nutrients in sweet almonds can play a role in the symptoms of ADHD, as mentioned above (49, 63).

Horse milk as a therapeutic substance in TIM has many therapeutic properties. The nutritional composition of horse milk differs from that of cow's milk in that it contains lower amounts of fat, cholesterol, and casein (milk protein). Studies have shown that the distribution of triglycerides and diglycerides in horse milk is similar to that of human milk. Furthermore, horse milk has a higher proportion of polyunsaturated fatty acids (PUFA) than both human and cow milk. Based on its structural characteristics and nutritional composition, horse milk may be more suitable for human consumption and infant formula than cow's milk, and because of the high content of omega-3, especially linoleic acid, can be effective in reducing symptoms of hyperactivity (28).

Four herbal medicines, *P. incarnate, C. sativus*, sweet almond syrup, and whey protein in combination with MPH or alone showed positive effects in reducing the severity of hyperactivity symptoms, inattention, and total score based on a Conner's rating scale, SDQ, and CPT (21, 25, 26, 37). About *G. Biloba*, the findings were contradictory. In one study, there was a significant reduction in the severity of symptoms of this disorder after supplementing with *G. biloba* (23), but in the second study, no significant improvement was observed (24).

The side effects of selected herbal remedies were very limited. ADHD can be a lifetime problem, the treatments in these studies were short-term (6 and 8 weeks.), and then some issues such as tolerance, long-term side effects, etc. are unclear.

The small number of study samples is considered a limitation of the present review study. This systematic review as secondary research can have limitations, including that it cannot answer all the questions raised in this field, and it is possible that there is a lack of precision in the analysis of the point of view.

Conclusion

The herbal remedies based on TIM might be effective in treating the core symptoms of ADHD**.** In TIM, other herbal formulations have been mentioned, which may be used to reduce the symptoms of ADHD that have not been studied so far and can be mentioned as a suggestion for researchers.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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