Synergistic Effects of Multiple Bioactive Ingredients in the Treatment of ADHD in Children: A Pathophysiological and Clinical Systematic Review

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KEYWORDS

ADHD, bioactive ingredients, children, efficacy, herbal medicine, systematic review

ABSTRACT:

Background and Objectives: Attention Deficit Hyperactivity Disorder (ADHD) is a complex neurodevelopmental disorder that affects the ability to pay attention, control hyperactivity, and regulate impulses. The utilization of a multiple bioactive ingredient formula (MBIF) comprising a mixture of natural substances has potential as an alternative intervention for individuals with ADHD. This systematic review aimed to assess the effectiveness and safety of MBIF in managing ADHD symptoms in children. Methods: A systematic search was conducted in MEDLINE (PubMed), Scopus, Web of Science (WOS), EMBASE, Google Scholar, JSTOR, and Cochrane databases to evaluate the efficacy of MBIF in treating children with ADHD. The extracted data included study title, author/authors, publication year, study design, target population, and findings. Results: Twelve studies met the inclusion criteria. The interventions included combinations of ADHD medications with supplements such as zinc (Zn), magnesium (Mg), and herbal extracts like Bacopa monnieri. Results varied, with some studies showing significant improvement in ADHD symptoms with the addition of bioactive ingredients, while others did not find significant differences. Conclusion: MBIFs may offer some benefit in managing ADHD symptoms, particularly when combined with standard medications. However, the effectiveness varies based on the type and combination of ingredients used. Further large-scale, high-quality RCTs are needed to confirm these findings.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a widespread neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity. These symptoms may greatly hinder an individual's ability to perform well in academic, vocational, and social settings (1, 2). Approximately 7.6% of children aged 3 to 12 years and 5.6% of adolescents aged 12 to 18 years worldwide are affected by ADHD, which often persists into adulthood and results in enduring challenges across several life domains (3). This is a complicated condition with multiple etiologies, including genetic, environmental, and neurological components (4). Various traditional treatment options include pharmacotherapy, cognitive-behavioural therapy, as well as individual and family counseling. Conventional therapies, which include a wide range of drugs, often result in adverse effects such as sleeplessness, reduced appetite, tiredness, high blood pressure, headache, mood changes, and convulsions. Therefore, there is a growing trend toward alternative therapies, including Multiple Bioactive Ingredients Formula (MBIF), mostly due to affordability and reduced potential for adverse effects (5).

1.1.Multiple Bioactive Ingredients Formula (MBIF)

Multiple Bioactive Ingredients Formula (MBIF), a blend of plant and natural ingredients with neuroprotection-enhanced cognitive abilities, has the potential to be a proper approach to the treatment of ADHD. This formula makes use of both additive and synergistic principles, where all ingredients provide a complete solution for managing ADHD symptoms (6, 7). Research on bioactive ingredients for the management of ADHD symptoms has shown promising results. Research has emphasized the potential advantages of many substances, including Bacopa monnieri, which has shown promising evidence of its effectiveness in alleviating ADHD symptoms (8). Similarly, acetyl-L-carnitine (ALC or ALCAR) has been examined to determine its efficacy in reducing symptomatology in children and adolescents with ADHD (9). Furthermore, zinc (Zn) and magnesium (Mg) have been proposed as potential supplements to address nutritional deficiencies associated with ADHD (10). Additionally, the safety and effectiveness of MBIF therapies, particularly in pediatric populations, need additional investigation.

2. OBJECTIVE

The systematic review on MBIFs for treating ADHD in childhood period aims to: 1) Examine how well MBIFs generally work to lower ADHD scores of symptoms. 2) Assess MBIF's safety profile, taking into account any unfavourable effects of its use. 3) Investigating differences in

treatment effects resulting from various MBIF compositions. 4) Specifying gaps in the existing literature and recommend futuristic research implications.

3. MBIF Relationship with Pathophysiologic Mechanisms in ADHD

3.1. Neuro-inflammation

One important pathophysiological factor of ADHD is neuro-inflammation, which may be minimized through bioactive compounds such as luteolin and honey extract. Strong antioxidant luteolin has been linked to anti-inflammatory effects that may lessen the neuroinflammation linked to ADHD (11). Comparably, honey extract, which is well-known for its wide-ranging antioxidant properties, may likewise control brain inflammatory responses (12). Omega-3 fatty acid-enriched phosphatidylserine has been investigated for use in ADHD treatment via multiple modes like neuroplasticity, neurotransmitter control, and anti-inflammatory properties, it is proposed to reduce ADHD symptoms (13). Clinical studies have shown that it works well to help ADHD youngsters with impulsivity/hyperactivity and inattention (14).

3.2. Cerebral Hypoperfusion

The cognitive abilities of individuals with ADHD are negatively impacted by reduced blood flow in the brain (15). Both blood flow in the brain and natural substances like Ginkgo biloba and citicoline can improve these cognitive abilities (16). Citicoline is especially noteworthy because it has the potential to enhance cerebral blood flow and cognitive performance in individuals with ADHD, thanks to its recognized neuroprotective effects (17).

3.3. Dysregulated Mitochondrial Function

Dysregulated Mitochondrial Function affects people with ADHD significantly via turbulence on brain physiology and energy metabolism, which may change cognitive abilities and everyday quality of life (18). Coenzyme Q10 (Co-Q10) is one of the bioactive compounds that has a leveraging effect on mitochondrial energy output and may improve the control of the symptomatology of ADHD (17).

Arnold et al. (2007) investigated the efficacy of ALC compared to a placebo in individuals with the inattentive subtype of ADHD. They found that ALCAR was successful in treating this subtype (19). Furthermore, research has demonstrated that ALC can reduce impulsive behavior. Nevertheless, the effectiveness of combining it with conventional ADHD medications such as methylphenidate did not yield significant enhancements (20). Modulation of fatty acid metabolism and mitochondrial function (two processes essential to energy generation and brain cellular functions) is one of the proposed causes of ALC (21).

3.4. Micronutrient Deficiency

Micronutrient Deficiency is prone to arise in persons afflicted by ADHD, particularly to Mg and Zn (22). Mg enhances synaptic function (23), hence helping to reduce the growth of ADHD symptoms such as impulsivity and hyperkinetic behavior (24). In addition, Zn showed a beneficial impact on attention as well as enhancement in neurocognitive function (25). The effectiveness of Zn has a positive impact on attention and working memory, as shown by El-Bakry et al. (2019). Administering Zn to children with ADHD and Zn deficiency has been shown to improve working memory and enhance scores on Conner's subscale (26).

3.5. Elevated Oxidative Stress

The disturbance in neurophysiology associated with ADHD is due to oxidative stress imbalance and antioxidants. Bioactive such as phosphatidylserine and Bacopa monnieri reduce oxidative stress and enhance the performance of working memory and inattention in ADHD patients by establishing a neuroprotective environment as a result of antioxidant activity (11, 12). Studies showed that the phosphatidylserine is considered beneficial for ADHD treatment, particularly in children aged 3 to 10, due to its compatibility and positive effects on cognitive function (27). Additionally, clinical trials suggest that Bacopa monnieri improves cognitive functions, emotional regulation, and attention, which are often impaired in ADHD (28).

3.6. The Validity of MBIF Targeting Pathophysiologic Mechanisms ADHD Management

Compelling clinical data supports the relationship, via pathophysiologic processes, between MBIFs and ADHD treatment. The complex character of ADHD is addressed therapeutically by the use of bioactive substances such as antioxidants, citicoline, and Bacopa monnieri. The integrated therapeutic strategy antagonizes the multiple pathophysiologic factors involved in ADHD pathomechanisms and relies on bioactive compound(s) that target oxidative stress, dysregulated mitochondrial function, and cerebral blood supply (11, 17, 25).

4. METHODS

This study was planned, structured, and carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria and the Cochrane Collaboration standards (29). These guidelines ensure transparency and reproducibility in systematic reviews by providing a comprehensive framework for conducting and reporting the studies. The review process involved careful planning, including the development of a detailed protocol, setting clear inclusion and exclusion criteria, and outlining precise data collection methods to maintain consistency and minimize bias.

4.1. Outcome Measure

Symptom Assessment: Studies have to assess ADHD symptoms—such as inattention, hyperactivity, and impulsivity exactly as they are specified in the most recent Diagnostic and

Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) versions. This ensures that the evaluation of ADHD symptoms is standardized and comparable across different studies. By adhering to these established diagnostic criteria, the review aims to accurately reflect the effectiveness of MBIFs in treating ADHD symptoms.

4.1.1. Primary Outcomes (Measurement of ADHD Symptoms)

Measuring symptoms directly using validated and standardized tools is crucial to determining how well ADHD medications work. The main signs of ADHD as listed in the ICD or the DSM should be matched by these tests. Research has underlined the need to use such uniform criteria to guarantee the accuracy and dependability of ADHD evaluations in various contexts and populations (30).

Approved Instruments for ADHD Symptom Measurement:

Conners' Parent Rating Scale-Revised (CPRS-R): This tool is widely used to assess behavioral changes in children with ADHD. It covers various aspects of behavior and can directly correlate with ADHD symptoms as defined in DSM and ICD criteria (31).

ADHD Rating Scale-IV (ADHD-RS-IV): This scale specifically measures the extent of symptoms according to the DSM criteria for ADHD, making it highly relevant for clinical trials and assessments. It includes questions that reflect both inattentive and hyperactive/impulsive behaviors, allowing for a comprehensive understanding of the severity and range of the disorder (32).

4.1.2. Secondary Outcomes

Reports or observational data (e.g., parent comments, teacher reports and clinician observations) that indirectly gauge how ADHD symptoms affect daily and quality of life (QoL). Such observational data can help validate quantitative findings and provide additional information on the treatment's efficacy and safety.

4.2. Search Strategies

The Authors conducted a search using seven electronic databases: MEDLINE (PubMed), Scopus, Web of Science (WOS), EMBASE, Google Scholar, JSTOR, and Cochrane Central Register of Controlled Trials. The search covered relevant studies published between 2003 and 2023. The search strategy followed the PICOD framework and involved identifying relevant keywords and their synonyms, which were organized in Table 1. The search terms were combined using Boolean operators to create different keyword combinations. Terms in different columns were connected with "AND," while terms in the same column were connected with "OR." Comprehensive information on the search keywords and databases is available in Appendix 1.

Table 1. Search strategies in the PICOD framework.		
PICOD	**Descriptors of the PICOD**	**Strategy**
Population (P)	ADHD patient	"Attention Deficit Hyperactivity Disorder" OR "ADHD" OR "Attention Deficit Disorder" OR "Attention Deficit Disorders with Hyperactivity" OR "Attention Deficit Hyperactivity Disorders" OR "Attention Deficit-Hyperactivity Disorder" OR "Brain Dysfunction, Minimal" OR "Minimal Brain Dysfunction"
Intervention (I)	Multiple Bioactive Ingredients	"Luteolin" OR "3',4',5,7-Tetrahydroxy-Flavone" OR "3',4',5,7-Tetrahydroxyflavone" OR "Cyticholine" OR "Phosphatidylserine" OR "Phosphatidyl Serine" OR "Phosphatidyl Serines" OR "Serine Phosphoglycerides" OR "Zizyphus Honey Extract" OR "Zizyphus Honey" OR "Bacopa Monnieri" OR "Acetyl-L-Carnitine" OR "Acetyl Carnitine" OR "Acetylcarnitine, (R)-Isomer" OR "Alcar" OR "ALC" OR "Levocarnitine Acetyl" OR "Medosan" OR "Magnesium" OR "Zinc"
Counter intervention (C)	No bioactive ingredients	-
Outcome (O)	Measurable outcomes of treatment	"Inattention" OR "Hyperactivity" OR "Impulsivity" OR "Impulsive Behavior" OR "Behavior" OR "QoL" OR "Quality of Life" OR "Health-Related Quality Of Life" OR "Life Quality"
Design (D)	Experimental studies	"Clinical trial", OR "open-label studies", OR "controlled clinical trial", OR "randomized clinical trial", OR "phase III clinical trial"

This review used certain factors as selection criteria for publications, shown in a PRISMA flowchart (Figure 1). Inclusion Criteria: English publications between 2012, and 2023, on MBIFs including herbs and bioactive ingredients for treating ADHD symptoms in children and adolescents. Human subjects are a mandatory condition. Efficacy and/or effectiveness ought to be reported for the MBIF. Exclusion Criteria: Animal experiments, reviews, research with small sample sizes, and articles written in languages other than English.

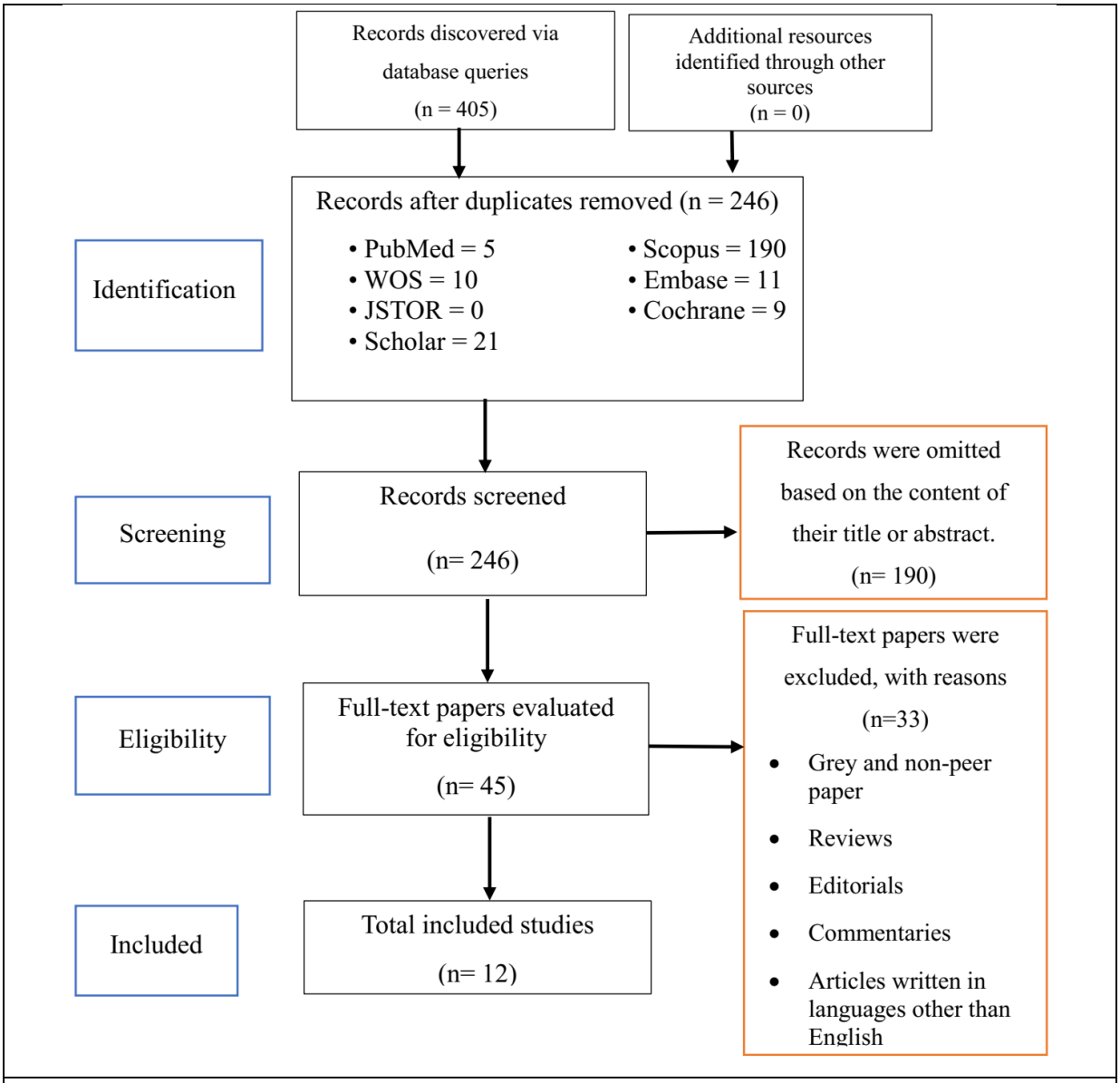


Figure 1. Flow diagram of our review process (PRISMA)

4.3. Data Collection

Every obtained piece of literature was examined by closely examining the title and abstract. Only the articles that matched the inclusion requirements were thoroughly evaluated, taking into account their whole contents. The authors independently extracted the relevant demographic and intervention characteristics using a standardized data extraction procedure for the research that matched the selection criteria. The writers settled any dispute on this matter through a discussion and exchange of viewpoints.

4.4. Quality assessment

Two independent members of the study team assessed the quality of the included articles using the Cochrane risk of bias tool for randomized clinical trials (RCT) in Review Manager 5 software

version 5.2, which is a method for evaluating the quality of RCT studies. This tool includes 6 parameters that are scored based on (Low risk, Unclear risk, and High risk).

4.5. Data Extraction

Data extracted from the studies included investigator details, publication year, research design, participant demographics, intervention specifications (composition, dosage, and duration), outcome metrics (affection scales, assessment instruments), results related to the reduction of ADHD symptoms, safety outcomes, and any adverse events reported. The concept of a Multiple Bioactive Ingredients Formula (MBIF) typically refers to a supplement that combines various active ingredients to address pathophysiologic mechanisms in ADHD has gained interest as researchers explore how natural compounds might impact the neurological and biochemical pathways involved in ADHD.

5. RESULTS

5.1. Literature Search

The literature search yielded 405 non-redundant literature records, of which 246 were chosen once duplicate research were eliminated. From 246 studies, 190 records were excluded based on the content of the title or abstract. A 45 full-text records were assessed for eligibility. Of these, 33 items were excluded due to gray and non-peer papers, reviews, editorials, commentaries, and articles written in languages other than English. Finally, based on the inclusion criteria, 12 records were included in the present study. The PRISMA flow chart for the systemic review is shown in Figure 1. Table 2 shows the information and results of the selected studies. Table 3 shows the ingredients of MBIF, active compounds, and their effects. The Cochrane analysis of bias risk is shown in Figure 2. Figure 3 illustrates the number of participants examined in the respective publications. Figure 4 shows the gender distribution of participants.

5.2. Standard of the Research

The studies included generally adhered to rigorous methodologies, with most being randomized, double-blind, and placebo-controlled, which minimizes bias and enhances the reliability of the results. However, the sample sizes varied, with some studies having fewer than 50 participants, possibly affecting the generalizability of the findings. The treatments ranged in length, spanning from six weeks to six months.

5.3. Results on MBIF Effectiveness in ADHD Management

The systematic review analyzed multiple studies focusing on the effectiveness of various bioactive ingredients, often components of MBIF, in the management of ADHD. Abbasi et al. (2011) investigated the combination of ALC with methylphenidate, finding no significant improvement in ADHD symptoms compared to the control group (33). Conversely,

Akhondzadeh et al. (2004) reported significant improvement in ADHD symptoms with the addition of Zn to methylphenidate treatment (34). Arnold et al. (2007) also studied ALC but did not observe a significant difference overall, though there was some evidence suggesting subtype-specific effects (19). Dave et al. (2014) utilized full Bacopa monnieri and reported substantial improvements across various ADHD symptoms, marking a promising result for herbal components in MBIF (35). Similarly, Bilici et al. (2004) (36), and Digirolamo et al. (2010) highlighted the positive effects of Zn supplementation in ADHD management, though Digirolamo et al. noted no significant behavioral changes but an association between Zn levels and improved mental health outcomes (37). Hemamy et al. (2021) investigated a combination of Vitamin D and Mg, showing significant reductions in multiple ADHD-related difficulties (38). Hirayama et al. (2014) found that phosphatidylserine significantly improved both cognitive functions and behavioral symptoms of ADHD (39). Manor et al. (2013) (13), and Noorazar et al. (2021) (40), also supported the efficacy of phosphatidylserine and Mg, respectively, in improving ADHD symptoms when combined with standard treatments.

Table 2. Detailed information on the included studies

Authors (year)	Design	Participants	Intervention	Measurements	ADHD Symptoms and Score	Adverse events
(01) Abbasi et al., 2011 (33)	Randomized, double-blind, placebo-controlled clinical trial	• Total: 40 outpatients (28 boys, 12 girls) • Group 1 (ALC + methylphenidate): 20 (13 boys, 7 girls); Age: 8.84 ± 2.03 years • Group 2 (Placebo + methylphenidate): 20 (15 boys, 5 girls); Age: 8.36 ± 1.53 years	• Group 1: ALC (ALC) 500-1,500 mg/day (based on weight) + methylphenidate 20-30 mg/day • Group 2: Placebo + methylphenidate 20-30 mg/day Duration: 6 weeks	• Parent and Teacher ADHD Rating Scale-IV (ADHD-RS-IV) • Side effects checklist	• No statistically significant difference was seen between the groups on the Parent and Teacher ADHD-RS-IV assessments. • The research did not endorse the use of ALC as an adjuvant treatment to methylphenidate in pediatric and adolescent populations with ADHD.	Headache (4 (case) vs 12 (control) and irritability (10 vs 18) were observed more frequently in the methylphenidate + placebo group
(02) Akhondzadeh et al., 2004 (34)	Double-blind, placebo-controlled randomized trial	• 44 children (40 completed) • Group 1 (Zn): 22 (14 boys, 8 girls), mean age 8.04 ± 1.73 years • Group 2 (Placebo): 22 (12 boys, 10 girls), mean age 7.73 ± 1.63 years	• Group 1: methylphenidate 1 mg/kg/day + Zn sulfate 55 mg/day (15 mg Zn element) • Group 2: methylphenidate 1 mg/kg/day + placebo (sucrose 55 mg) Duration: 6 weeks	• Teacher ADHD Rating Scale • Parent ADHD Rating Scale	• Both measures demonstrated statistically significant enhancements in the Zn group vs to the placebo. • Parent ADHD Rating Scale: - Greater improvement in the Zn group (F=4.15, df=1, p=0.048) - Significant difference between groups at endpoint (p=0.0009) • Teacher ADHD Rating Scale:	Most common side effects: • Metallic taste: 13 (Zn) vs 0 (placebo) • Nausea: 9 (Zn) vs 3 (placebo) • Abdominal pain: 8 (Zn) vs 4 (placebo)

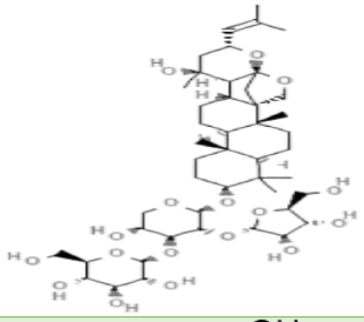
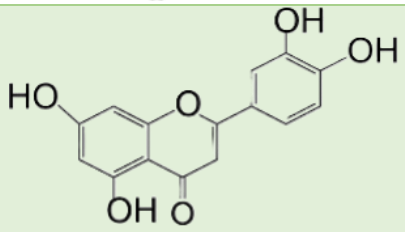
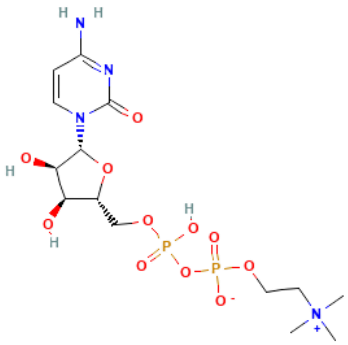
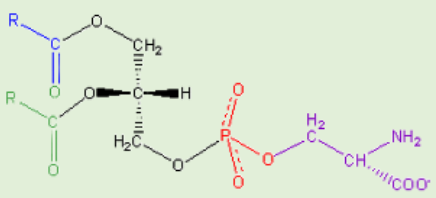
					- Greater improvement in the Zn group (F=4.50, df=1, p=0.04) - Significant difference between groups at endpoint (p=0.0009)	
(03) Arnold et al., 2007 (19)	Multi-site, parallel-group, double-blind randomized placebo-controlled pilot trial	• Total n=112 • Placebo: n=59, age 8.3 ± 2.2 years, 42 boys (71%), 17 girls (29%) • ALC: n=53, age 8.4 ± 2.3 years, 41 boys (77%), 12 girls (23%)	• ALC vs placebo • Dose: 500-1500 mg twice daily based on weight: 13.5-30 kg = 0.5 g b.i.d. >30-50 kg = 1.0 g b.i.d. >50 kg = 1.5 g b.i.d. • Duration: 16 weeks	• Conners' revised long version parent and teacher scales DSM-IV ADHD symptoms (9 inattentive, 18 total) • Clinical Global Impressions (CGI) scale	• No statistically significant difference was seen between the ALC and placebo groups for the main outcome of teacher-assessed inattention or secondary measures. • Primary outcome (teacher-rated 9 inattentive symptoms): No significant difference. • Significant moderation by ADHD subtype (p=0.02): ALC superior to placebo in the inattentive type, opposite tendency in the combined type Geographic effect observed (p=0.047)	Most of the observed side effects were: • Adverse Events–Related (12 (cases) vs. 15 (controls)) • Adverse Events–Any (40 vs. 44) •Gastrointestinal Disorders (16 vs. 11) • Headache (11 vs. 5) • Infections and Infestations (8 vs. 16)
(04) Bilici et al., 2004 (36)	Double-blind, placebo-controlled study	•N = 400; 72 girls, 328 boys, mean age = 9.61 F1.7) • Control Group: 198 (Mean age: 9.7 ± 1.8 years, 32 girls, 166 boys) • Intervention Group: 202 (Mean age: 9.4 ± 1.5 years, 40 girls, 162 boys)	Zn sulfate (150 mg/day) for 12 weeks	• ADHD Scale (ADHDS) • Conners Teacher Questionnaire • DuPaul Parent Ratings of ADHD	• The Zn sulfate group exhibited a significant decrease in hyperactivity, impulsivity, and socializing deficits relative to the placebo ($p < 0.05$). • No significant reduction in attention deficiency symptoms. • Full therapeutic response rates: 28.7% (Zn) vs. 20% (placebo)	• Zn sulfate was well tolerated The most reported adverse effects: • Metallic taste (50 participants in the Zn group compared to 8 participants in the placebo group) • Nausea (8 vs. 7) • Vomiting (5 vs. 4)
(05) Dave et al., 2014 (35)	Open-label study	Total: 31 children (27 completed the trial), (28 males and 3 females) 6-12 years	•Composition: Standardized Bacopa monnieri extract (BacoMind) • Dose: 225 mg/day • Duration: 6 months	Parent Rating Scale for ADHD symptoms	• A drop of up to 20% in overall subtest scores: Seventy-four percent of children. • 21-50% reduction in total subtest scores: 26% of children. •Restlessness: 93% reduction • Self-control: 89% improvement • Attention deficit: 85% reduction	• No significant adverse effects reported. • SBME was well-tolerated by the children

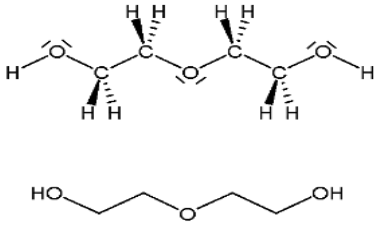
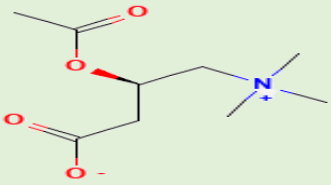
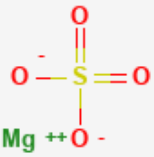
					• Learning problems: 78% reduction • Impulsivity: 67% reduction • Psychiatric problems: 52% reduction	
(06) Digirolamo et al., 2010 (37)	Randomized, double-blind, placebo-controlled trial	• 674 children • Zn group: 343 (174 males and 169 girls, 9.0 ± 1.2) • Placebo group: 331 (163 males and 168 girl, 8.9 ± 1.2)	• Zn supplementation: 10 mg ZnO/day, 5 days/week for • Placebo: 10 mg glucose/day, 5 days/week for	• Children's Depression Inventory (CDI) • Revised Children's Manifest Anxiety Scale (RCMAS) • Parental reports on behavioral symptoms	• The Zn and placebo groups exhibited no significant differences in any behavioral parameters at baseline or follow-up. •Elevations in blood zinc concentrations were negatively correlated with reductions in depressive symptoms, anxiety, internalizing symptoms, and social skills in adjusted models that accounted for child age, sex, socioeconomic position, household, and treatment group.	No significant complications reported
(07) Hemamy et al., 2021 (38)	Double-blind, randomized controlled trial	• 66 children with ADHD (9.11 ± 1.61 years) • Intervention group: 33 (23 boys and 10 girls, 9.06 ± 1.76) • Control group: 33 (23 boys and 10 girls, 9.15 ± 1.46)	• Case Group: Vitamin D (50,000 IU/week) + Mg (6 mg/kg/day) for 8 weeks • Control Group: placebo	Strengths and Difficulties Questionnaire	• Significant decrease in emotional problems (p=0.001), conduct problems (p=0.002), peer problems (p=0.001), prosocial score (p=0.007), total difficulties (p=0.001), externalizing score (p=0.001), and internalizing score (p=0.001)	No side effects reported
(08) Hirayama et al., 2014 (39)	Randomized, double-blind, placebo-controlled clinical trial	• 36 children (34 males and 2 females) • Intervention group: 19 children (18 males and 1female) (mean age 9.1 ± 1.7 years) • Control group: 17 children (16 males and 1 female) (mean age 8.7 ± 3.0 years)	200 mg/day of soy-derived phosphatidylserine for 2 months	• ADHD symptoms based on DSM-IV-TR • Short-term auditory memory and working memory assessed by the Digit Span Test of the Wechsler Intelligence Scale for Children. • Mental performance to visual stimuli (GO/NO GO task).	• Overall ADHD symptoms: $P < 0.01$. Significant improvements in ADHD symptoms: • Inattention: $P < 0.05$ • Hyperactivity: $P < 0.01$ • Impulsivity: $P < 0.01$ • Short-term auditory memory: $P < 0.05$	No significant adverse events were reported; PS was well-tolerated.
(09) Manor et al., 2013 (13)	Double-blind placebo-	• 200 children (133 boys, 67	• Double-blind phase: The PS-	• Safety parameters: blood	No notable alterations from baseline were seen in any of the	No significant differences

	controlled trial	girls) aged 6-13 years • Case group: 137 (9.2 ± 2.0) • Control group: 63 (9.2 ± 1.8)	Omega 3 group received 300 mg PS + 120 mg EPA/DHA per day. The placebo group receives cellulose capsules. • Open-label extension: All participants received 150 mg PS + 60 mg EPA/DHA per day	biochemical and hematological variables, blood pressure, heart rate, weight, and height. • Side Effect Rating Scale (SERS).	examined parameters among subjects who ingested PS-Omega3 for 30 weeks.	in safety parameters between groups.
(10) Noorazar et al., 2020 (41)	Double-blind randomized clinical trial	• 60 children (48 boys, 12 girls, 9.69 ± 1.70 years) • Control group: 30 (20 boys and 10 girls, 9.30 ± 1.38) • Case group: 30 (28 boy and 2 girl, 8.87 ± 1.97)	• Control Group: (0.5-1 mg/kg/day) + Placebo • Case Group: methylphendiate (0.5-1 mg/kg/day) + 10 mg Zn (10 cc Zn sulfate syrup)	Connors Parent's Questionnaire	• No substantial change was seen between the two groups post-intervention for the overall score. • No notable variation in the hyperactivity and impulsivity subscales. Notable enhancement in inattention score among the case group (p=0.02)	No adverse events reported
(11) Noorazar et al., 2021 (40)	Double-blind randomized clinical trial	• 40 children in total • Intervention group: 20 (Mean age: 9.0 ± 1.6 years, 13 boys, 7 girls) • Control group: 20 (Mean age: 9.3 ± 1.4 years, 14 boys, 6 girls)	• Intervention group: methylphenidate (0.5-1 mg/kg/d) + Mg (10 mg/d) for 8 weeks • Control group: methylphenidate (0.5-1 mg/kg/d) + Placebo for 8 weeks	Conner's Parent Rating Scale	• A notable disparity between the two groups on Conner's Parent Rating Scale post-intervention (P=0.02) • Significant reduction in ADHD symptoms in the intervention group compared to the control group (P=0.02 for total score, P=0.001 for inattention subscale)	No serious side effects were reported. Minor adverse events included: Nausea and vomiting: Intervention: 3 (15%), Control: 2 (10%) Headache: Intervention: 1 (5%), Control: 2 (10%) Decreased appetite: Intervention: 1 (5%), Control: 1 (5%) sleep disorder: Intervention: 1 (5%), Control: 2 (10%)
(12) Salehi et al., 2016 (42)	Randomized, double-blind clinical trial	• 150 children aged 6-15 years with ADHD • Control group: 50 (32 boys, 18 girls, mean age	• Control: methylphenidate + placebo • Zn: methylphenidate + 22 mg	Conners' Parent and Teacher Rating Scales	• Significant decrease in Conners' scores over time for all groups (P < 0.01) • No significant differences among	No serious adverse events reported.

		9.12 ± 2.2 years) • Zn group: 50 (40 boys, 10 girls, mean age 9.5 ± 2.5 years) • Omega-3 group: 50 (39 boys, 11 girls, mean age 8.6 ± 1.7 years)	Zn sulfate daily • Omega-3: methylphenidate + 100-400 mg omega-3 daily (based on weight)		groups at baseline (P = 0.07) • Significant improvement in Zn group vs control (P = 0.02) • Omega-3 showed better clinical response than Zn (P = 0.03) but not significantly different from control (P = 0.89)	

Table 3. Active constituents present in the listed MBIF

Name of the MBIF	Active Constituent	Effect	Chemical Structure
Bacopa monnieri	Bacopaside I	*Bacopa monnieri*, often known as brahmi, is a plant that is extensively used in Ayurvedic medicine (43). In the context of ADHD, full spelling is sometimes considered for its potential to improve attention and memory (44).	
Luteolin	Luteolin	It has antioxidant and anti-inflammatory properties (45).	
Citicoline	cytidine 5'-diphosphocholine	It has been shown to have neuroprotective properties, which might be beneficial in conditions where there is increased oxidative stress or neuroinflammation (46).	
Phosphatidylserine	Phosphatidylserine	Phosphatidylserine is a phospholipid abundantly present in the brain, namely in the cell membranes of neurons. Phospholipids are essential for the integrity and proper functioning of cell membranes, as well as for transmitting signals and releasing neurotransmitters (47). In the context of ADHD, PS is sometimes considered for its potential neuroprotective	

		and cognitive-enhancing effects (48).	
Ziziphus Honey	Ziziphus Honey	Honey is abundant in antioxidants, which may aid in safeguarding the body from oxidative stress induced by free radicals (49).	
Acetyl-L-Carnitine	Form of L-carnitine	ALC, or ALCAR, is a naturally occurring derivative of an amino acid often used as a dietary supplement. It is recognized for its function in fatty acid metabolism and energy generation inside cellular mitochondria (50).	
Magnesium	Magnesium	Mg is known to be crucial for proper neurological function. It plays a role in synapse function and plasticity. It can also modulate the stress response system in the body (51).	
Zinc	Zinc	Zn is a vital mineral that plays a crucial role in several physiological processes, such as brain growth and the creation of neurotransmitters. Additionally, research has shown that it can regulate dopamine and norepinephrine pathways, exhibits antioxidant characteristics, and reduces inflammation (52, 53).	

Hirayama et al. (2014) found that phosphatidylserine significantly improved both cognitive functions and behavioral symptoms of ADHD (39). Manor et al. (2013) (13), and Noorazar et al. (2021) (40), also supported the efficacy of phosphatidylserine and Mg, respectively, in improving ADHD symptoms when combined with standard treatments.

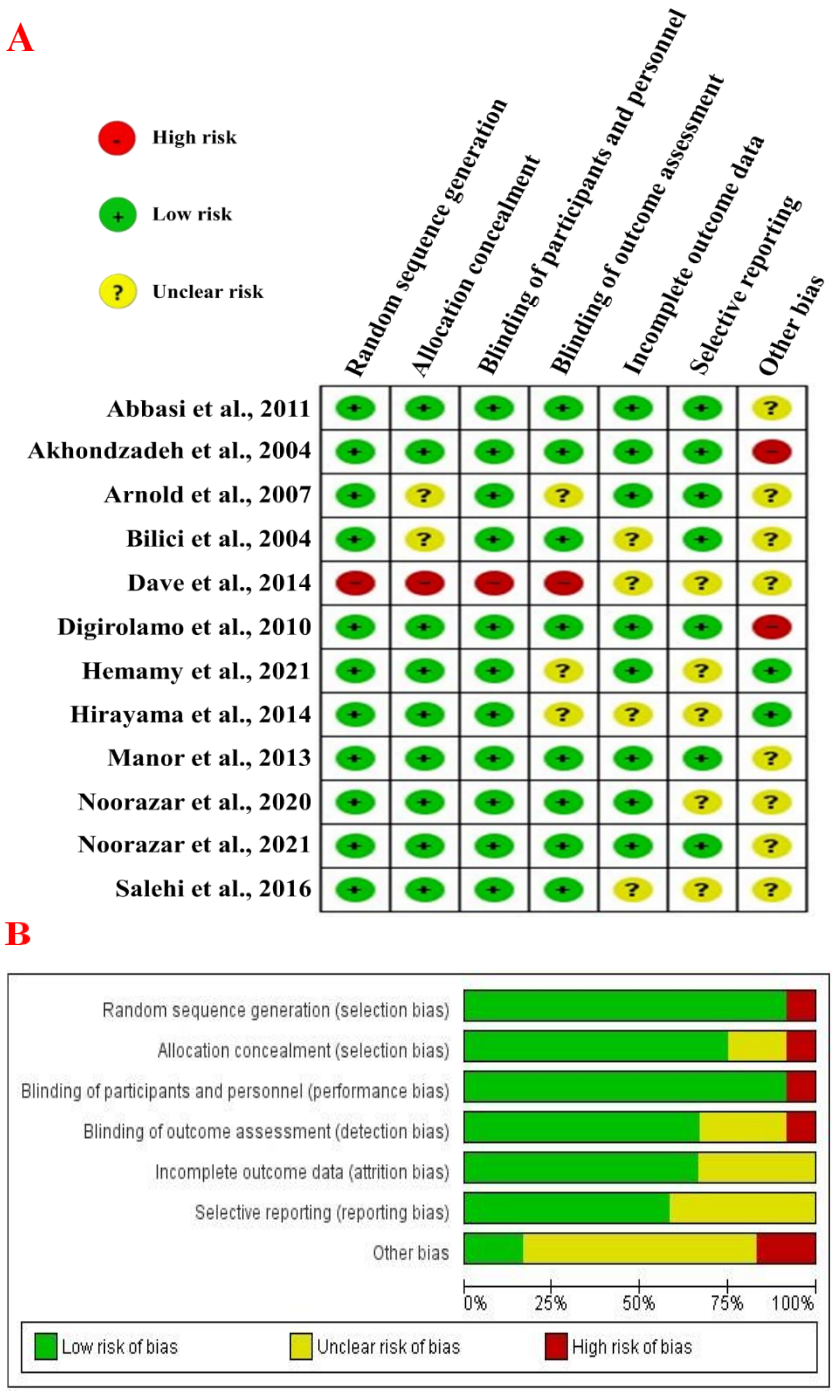


Figure 2. (A) Assessment of risk of bias. (B) Risk of bias graph

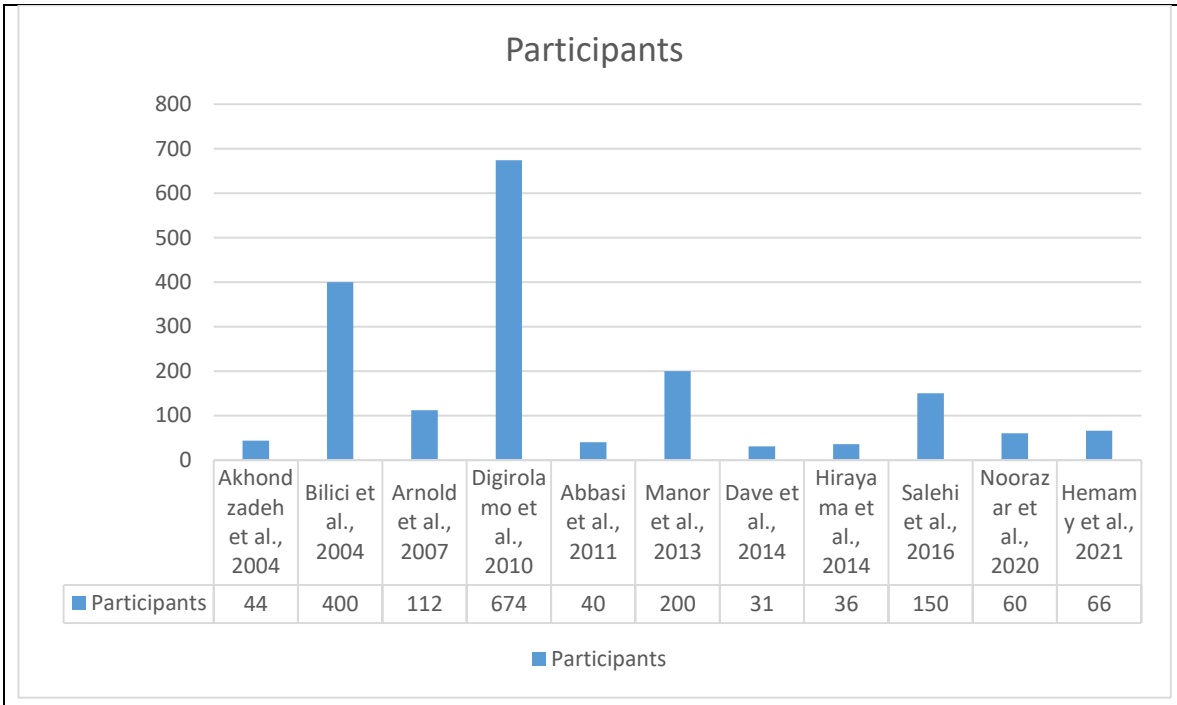


Figure 3. Bar plot of the number of individuals under study in the included studies.

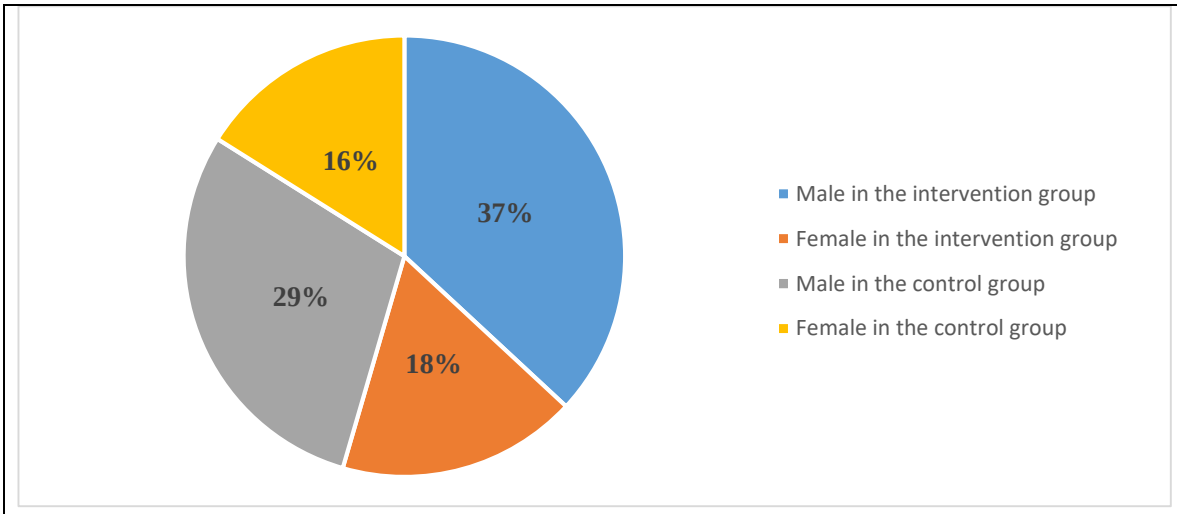


Figure 4. Separation of participants based on gender.

5.4. MBIF Safety Profile

Regarding the safety profile, most studies reported that MBIF components were well-tolerated with minimal adverse effects. Specific studies like Dave et al. (2014) (35), and Hemamy et al. (2021) explicitly noted the absence of significant adverse events, underscoring the potential for the safe use of MBIF in children with ADHD (38). Bilici et al. (2004), while noting improvements with Zn supplementation, reported higher incidences of a metallic taste, a

relatively benign side effect (36). Similarly, minor gastrointestinal complaints were the most commonly reported adverse effects in studies utilizing Zn and Mg.

5.5. Treatment Effect Variations According to MBIF Formulations or Compositions

The systematic review revealed varied responses to different components of MBIF in the treatment of ADHD among children. For instance, the efficacy of ALC was not consistent across studies, suggesting that its effectiveness might depend on specific formulation factors or patient characteristics such as the ADHD subtype, as suggested by Arnold et al. (2007) (19). In contrast, studies involving Zn consistently showed positive outcomes, hinting at a potentially more robust effect of this mineral in ADHD management across different study designs and populations.

6. DISCUSSION

This systematic review aimed to evaluate the effectiveness and side effects of MBIF on the management of ADHD in children. There were several focal areas as primary measures in these studies, including attention, hyperactivity, impulsivity, and patients' quality of life, while secondary measures were safety and patient tolerance of the proposed treatments together. Covered the bioactive including Acetyl-L-Carnitine, Zn sulfate, citicoline, Mg and phosphatidylserine, Bacopa monnieri and Luteolin

6.1. How do MBIFs affect ADHD?

6.1.1. Luteolin

Animal studies show that luteolin can modulate neurotransmitter systems, including dopamine and norepinephrine, which are strongly involved in the regulation of attention and behavior, so it promises a positive effect on ADHD (54). Luteolin’s ability to inhibit pro-inflammatory cytokines and oxidative stress could help in mitigating the neuroinflammatory state often observed in ADHD patients, thereby improving neuronal function and attentiveness (45, 55).

6.1.2. Citicoline

Citicoline is known to enhance the synthesis of phosphatidylcholine, a vital component of neuronal membranes, and boost brain neurotransmitters, particularly dopamine (56). In ADHD, where dopamine dysregulation is commonly implicated, citicoline may help improve dopamine functionality, which is essential for attention and cognitive control (57). Moreover, citicoline has been shown to enhance frontal lobe bioenergetics, thus potentially improving executive functions and attentional capacities in ADHD individuals (58).

6.1.3. Phosphatidylserine

This phospholipid component is integral to maintaining cellular function in the brain. Phosphatidylserine has been shown to stabilize the membrane of brain cells, enhancing overall cellular metabolism and neurotransmitter dynamics, including acetylcholine, serotonin,

norepinephrine, and dopamine (59, 60). By modulating these neurotransmitters, phosphatidylserine can potentially improve attention, memory, and emotional regulation in ADHD (60, 61).

6.1.4. Ziziphus Honey Extract

While specific studies on Ziziphus honey extract's effect on ADHD are limited, the general pharmacological properties include antioxidant and calming effects (62). The extract might modulate oxidative stress and provide a soothing effect on the central nervous system, which could be beneficial in managing hyperactivity and impulsivity symptoms associated with ADHD (63).

6.1.5. Bacopa monnieri

Bacopa monnieri extract is well-tolerated by children, with a reduction in attention-deficit symptoms seen in 85% of cases. Likewise, ratings for learning difficulties, impulsivity, and mental disorders decreased in 78%, 67%, and 52% of children, respectively (64).

Bacopa monnieri often used in Ayurvedic medicine for enhancing cognitive functions, may improve ADHD symptoms through several pathways (43). It is known to increase cerebral blood flow and modulate neurotransmitters like dopamine and serotonin, pivotal in ADHD pathophysiology (65). Also, Bacopa monnieri's antioxidant properties help reduce oxidative stress, potentially improving attention and processing speeds in ADHD (28). Research into Bacopa monnieri suggests that its influence on neurotransmitter modulation, particularly acetylcholine, may enhance attention and cognitive function (66). Its antioxidant and anti-inflammatory properties could also help alleviate oxidative stress and inflammation, potentially improving ADHD symptoms. Moreover, the herb's ability to enhance neuroplasticity may further support cognitive function in individuals with ADHD.

However, the empirical evidence supporting Bacopa monnieri's effectiveness in treating ADHD is currently limited. Most existing studies have small sample sizes, inconsistent dosing regimens, and varying methodologies, which complicate the interpretation of the results (67).

6.1.6. Acetyl-L-Carnitine (ALC)

The findings regarding acetyl-L-carnitine (ALC) indicate that, while it appears to be safe for use in the treatment of ADHD, it does not demonstrate significant effectiveness for the overall population (68).

ALC plays a crucial role in fatty acid metabolism in mitochondria, which is essential for energy production (69). Since ALC can help reduce oxidative stress and improve mitochondrial function, it can increase neurotransmission and overall brain function and have beneficial effects in ADHD (21, 70). This action can help in alleviating attention deficits and hyperactivity (21,

71). Consistent with Wang et al's findings, they showed that the LC had beneficial therapeutic benefits in the treatment of Alzheimer's disease (AD), carpal tunnel syndrome (CTS), CD, migraine, neurofibromatosis (NF), PNSDs, RS, and stroke. Nonetheless, its effectiveness seems to be somewhat restricted in disorders such as ALS, ataxia, ADHD, depression, chronic fatigue syndrome (CFS), Down syndrome (DS), and sciatica (72).

6.1.7. Mg

The results of the study by Farida et al., showed that the consumption of Mg in the intervention group reduced emotional problems and general problems after 8 weeks compared to the control group (73). Mg deficiency was found in 72% of children with ADHD, and supplementation improved cognitive functions. No major side effects were reported with this supplement, although common mild side effects included nausea (15%), headache (5%), decreased appetite (5%), and sleep disturbances (5%). Overall, 22.2% experienced mild abdominal discomfort and diarrhea (73). Mg is involved in numerous biochemical reactions in the body, including neurotransmitter release and receptor function (74). It has a soothing influence on the neural system, which may aid in regulating hyperactivity and impulsivity in children with ADHD. Additionally, Mg contributes to synaptic plasticity, which might enhance learning and memory, often compromised in ADHD (24). The results of Botturi et al.'s studies showed that Mg is an essential cation that plays a role in many functions of the central nervous system, including intracellular signal transmission, but considering that in some studies the results of this function are reported to be weak, the design of clinical trials ad hoc to evaluate the effectiveness of Mg alone or in combination with other drugs (antidepressants) is necessary to determine the correct use of this cation with potential therapeutic effects (75).

6.1.8. Zinc

Zinc plays a crucial role in neurological function, influencing neurotransmitter synthesis and brain health (76). Research indicates that children with ADHD often exhibit lower levels of Zn compared to their peers without the disorder (77). A study involving Zn-deficient children diagnosed with ADHD showed significant improvements in working memory and behavioral scores after 10 weeks of Zn supplementation (30 mg/day) alongside their usual medication methylphenidate (26). Zn supplementation is generally considered safe when recommended; however, potential side effects can occur. These may include nausea, vomiting, and diarrhea, which are common side effects associated with higher doses of Zn (78).

Zinc modulates synaptic neurotransmitter function and is critical for the metabolism of melatonin, which regulates dopamine function—a key neurotransmitter involved in the cognitive and emotional aspects of ADHD (79). Zn deficiency has been linked with poor neurologic

function, and supplementation might improve attention, activity, and impulsivity levels in ADHD patients (80). The findings of Lange et al. study were contrary to popular belief, indicating that zinc supplementation does not alleviate symptoms in patients. Furthermore, various studies reveal no statistically significant differences in hair and serum/plasma zinc levels between individuals with ADHD and control subjects (81).

6.2. Efficacy of MBIF in Managing ADHD Symptoms

The present study examined the effectiveness of MBIFs in the management of ADHD in children, focusing on a variety of single and combined supplements. The studies reviewed suggest a variable impact of these ingredients on ADHD symptoms, with some showing significant benefits while others do not support their use as effective treatments.

ALC, investigated in two studies, did not show significant differences in ADHD symptoms compared to placebo (19, 33). Dominique (2019) showed that administering ALC as a standalone treatment without any other drugs was ineffective and did not significantly improve youngsters' conduct and attention (82). Further investigations are required to explore these potential advantages, particularly in the context of the inattentive subtype.

Zinc is a micro-element that plays a crucial role in several neurological processes, including the metabolism of the neurotransmitters dopamine and serotonin (83). Some studies have linked low Zn levels to symptoms most related to ADHD, including memory problems, inattention, and impulsiveness (84). Akhondzadeh et al. (2004) (34), and Bilici et al. (2004) (36), demonstrated that Zn supplementation led to significant improvements in hyperactivity, impulsivity, and socialization symptoms.

Studies have also shown that phosphatidylserine offers great improvement in the symptoms of ADHD inattention, hyperactivity, and impulsivity (39, 85). Further research supports these outcomes, proving that phosphatidylserine intake considerably decreases inattention, impulsivity, and hyperactivity (86). However, Bruton et al. (2021) showed that the effects of phosphatidylserine on overall ADHD symptoms (effect size 0.76, p=0.07) and hyperactivity-impulsivity (effect size 0.24, p=0.09) were not statistically significant but tended to be positive (87). Similarly, a study by Manor et al. (2013) showed notable improvements in ADHD symptoms, including inattention and hyperactivity (13). These contradictory outcomes indicate the need for an extensive study to assess the impact of phosphatidylserine on ADHD.

In the current systematic review, Dave et al. (2014) performed an open-label trial that showed the efficiency of a standardized Bacopa monnieri extract in decreasing the severity of ADHD symptoms, such as hyperactivity and inattention, in children aged between 6 and 12 years. The study found significant improvements in ADHD symptom scores six months after Bacopa

monnieri supplementation (35). Research by Kean et al. (2015) found that a standardized Bacopa monnieri extract (CDRI 08) significantly improved measures of attention, concentration, and behavior in boys aged 6-14 years with high levels of inattention and hyperactivity. The study showed that Bacopa monnieri was effective in reducing ADHD symptoms compared to placebo (88).

Adding Mg, either by itself or with other minerals, has been linked to notable enhancements in cognitive abilities and symptoms related to ADHD (40, 41). When Mg is paired with vitamin D, there is a noticeable decrease in emotional and behavioral issues, better peer interactions, and fewer overall difficulties (38). These observations indicate that multi-nutrient interventions could positively affect cognitive performance and mental well-being in children diagnosed with ADHD.

6.3. Safety and Tolerability of MBIF

In terms of the safety and tolerability of MBIF, findings from various studies are favorable. ALC showed fewer intolerable side effects than methylphenidate, with side effects including headache and irritability being more frequent in the CG (19, 33). Zn sulfate administration has been reported to result in metallic taste and minor gastrointestinal disturbances (36). Mg supplementation has been linked to occasional mild side effects, including nausea and abdominal pain, although these were not severe (40). In addition, no side effects of phosphatidylserine have been reported during treatment (39). Based on these positive safety profiles, the bioactive compounds under discussion have the potential to be used as complementary therapies for ADHD. Nevertheless, it remains crucial to monitor for potential adverse reactions and adjust dosages as needed to safeguard the health of pediatric patients.

7. Conclusions

This systematic review thoroughly examines the potential benefits of (MBIFs) in managing ADHD among children. The evidence presented in the study reveals varied outcomes; in certain instances, it underscores notably promising results regarding the management of ADHD symptoms. Nevertheless, it is crucial to note that the overall efficacy and safety of these MBIF treatments may be influenced by several factors, including the specific formulations used, the doses administered, and the demographic characteristics of the participants involved in the studies.

To arrive at definitive conclusions regarding the effectiveness and safety of MBIFs for treating ADHD, future research must be conducted through standardized, well-controlled, and long-term studies involving a larger and more diverse population. Such rigorous studies would not only enhance our understanding of how MBIFs can be effectively integrated into ADHD treatment

protocols but also aid in optimizing treatment strategies. Ultimately, this approach has the potential to diminish the reliance on conventional pharmaceutical treatments, which frequently come with a higher risk of adverse side effects, thereby providing a safer and more holistic option for managing ADHD in children.

7.1. Literature Gaps and future research suggestion

The reviewed literature on MBIFs for managing ADHD in children reveals several significant gaps and limitations. Firstly, the studies did not take into account all relevant factors associated with MBIFs; only four were examined: Bacopa monnieri, Acetyl-L-Carnitine Mg, and Zn. This limited scope means other potentially important elements were overlooked.

Moreover, the studies produced inconsistent and sometimes contradictory results, complicating the ability to draw general conclusions. Many of the studies were hindered by small sample sizes and short durations, restricting the broader applicability of their findings.

There was also notable variation in the types of MBIF components studied and their formulations, which makes direct comparisons between studies challenging. Additionally, the reliance on reports from parents and teachers for outcome measures raises concerns about potential bias in the findings.

To address these limitations, future research should focus on incorporating objective measurements and extending follow-up periods. This approach will enhance the understanding of the effectiveness of MBIFs in treating ADHD. Additionally, conducting randomized controlled trials (RCTs) that isolate and measure individual factors in the treatment of ADHD will enable clearer conclusions about each factor's role in managing symptoms. Most existing studies have examined multiple factors together, making it difficult to evaluate their contributions. By focusing on single-factor analyses, researchers can better assess how each element influences ADHD management.

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Data availability: The corresponding author is available to provide the study's data upon a reasonable request.

Consent for publications: The authors reviewed and gave their approval to the published version of the study.

Authors' contributions: The authors contributed to this study work equally.

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Appendix

APPENDIX 1: SEARCH STRATEGY FOR EACH DATABASE (MEDLINE)		
Search ID#	Search terms	Results
#1	((((((((Attention Deficit Hyperactivity Disorder[Title/Abstract]) OR (ADHD[Title/Abstract])) OR (Attention Deficit Disorder[Title/Abstract])) OR (Attention Deficit Disorders with Hyperactivity[Title/Abstract])) OR (Attention Deficit Hyperactivity Disorders[Title/Abstract])) OR (Attention Deficit-Hyperactivity Disorder[Title/Abstract])) OR (Brain Dysfunction, Minimal[Title/Abstract])) OR (Hyperkinetic Syndrome[Title/Abstract])) OR (Minimal Brain Dysfunction[Title/Abstract])	44,796
#2	((((((((((((((((((Luteolin[Title/Abstract]) OR (3',4',5,7-Tetrahydroxy-Flavone[Title/Abstract])) OR (3',4',5,7-Tetrahydroxyflavone[Title/Abstract])) OR (Cyticholine[Title/Abstract])) OR (Phosphatidylserine[Title/Abstract])) OR (Phosphatidyl Serine[Title/Abstract])) OR (Phosphatidyl Serines[Title/Abstract])) OR (Serine Phosphoglycerides[Title/Abstract])) OR (Zizyphus Honey Extract[Title/Abstract])) OR (Zizyphus Honey[Title/Abstract])) OR (Bacopa Monnieri[Title/Abstract])) OR (Acetyl-L-Carnitine[Title/Abstract])) OR (Acetyl Carnitine[Title/Abstract])) OR (Acetylcarnitine, (R)-Isomer[Title/Abstract])) OR (Alcar[Title/Abstract])) OR (ALC[Title/Abstract])) OR (Levocarnitine Acetyl[Title/Abstract])) OR (Medosan[Title/Abstract])) OR (Magnesium[Title/Abstract])) OR (Zinc[Title/Abstract])	247,753
#3	((((((((Inattention[Title/Abstract]) OR (Hyperactivity[Title/Abstract])) OR (Impulsivity[Title/Abstract])) OR (Impulsive Behavior[Title/Abstract])) OR (Behavior[Title/Abstract])) OR (QoL[Title/Abstract])) OR (Quality of Life[Title/Abstract])) OR (Health-Related Quality Of Life[Title/Abstract])) OR (Life Quality[Title/Abstract])	1,331,084
#4	((((Clinical trial[Title/Abstract]) OR (open-label studies[Title/Abstract])) OR (controlled clinical trial[Title/Abstract])) OR (randomized clinical trial[Title/Abstract])) OR (phase III clinical trial[Title/Abstract])	220,379
#5	#1 AND #2 AND #3 AND #4	16

Scopus		
Search ID#	Search terms	Results
#1	(TITLE-ABS-KEY (attention AND deficit AND hyperactivity AND disorder) OR TITLE-ABS-KEY (adhd) OR TITLE-ABS-KEY (attention AND deficit AND disorder) OR TITLE-ABS-KEY (attention AND deficit AND disorders AND with AND hyperactivity) OR TITLE-ABS-KEY (attention AND deficit AND hyperactivity AND disorders) OR TITLE-ABS-KEY (attention AND deficit-hyperactivity AND disorder) OR TITLE-ABS-KEY (brain AND dysfunction, AND minimal) OR TITLE-ABS-KEY (brain AND dysfunction, AND minimal) OR TITLE-ABS-KEY (minimal AND brain AND dysfunction))	103,334
#2	(TITLE-ABS-KEY (luteolin) OR TITLE-ABS-KEY (cyticholine) OR TITLE-ABS-KEY (phosphatidylserine) OR TITLE-ABS-KEY (phosphatidyl AND serine) OR TITLE-ABS-KEY (phosphatidyl AND serines) OR TITLE-ABS-KEY (serine AND phosphoglycerides) OR TITLE-ABS-KEY (zizyphus AND honey) OR TITLE-ABS-KEY (bacopa AND monnieri) OR TITLE-ABS-KEY (acetyl-l-carnitine) OR TITLE-ABS-KEY (acetyl AND carnitine) OR TITLE-ABS-KEY (alcar) OR TITLE-ABS-KEY (alc) OR TITLE-ABS-KEY (levocarnitine AND acetyl) OR TITLE-ABS-KEY (magnesium) OR TITLE-ABS-KEY (zinc))	1,172,165
#3	(TITLE-ABS-KEY (inattention) OR TITLE-ABS-KEY (hyperactivity) OR TITLE-ABS-KEY (impulsivity) OR TITLE-ABS-KEY (impulsive AND behavior) OR TITLE-ABS-KEY (behavior) OR TITLE-ABS-KEY (qol) OR TITLE-ABS-KEY (quality AND of AND life) OR TITLE-ABS-KEY (health-related AND quality AND of AND life) OR TITLE-ABS-KEY (life AND quality))	7,090,559
#4	(TITLE-ABS-KEY (clinical AND trial) OR TITLE-ABS-KEY (open-label AND studies) OR TITLE-ABS-KEY (controlled AND clinical AND trial) OR TITLE-ABS-KEY (randomized AND clinical AND trial) OR TITLE-ABS-KEY (phase AND iii AND clinical AND trial))	2,284,157
#5	#1 AND #2 AND #3 AND #4	207

EMBASE		
Search ID#	Search terms	Results
#1	'attention deficit hyperactivity disorder':ab,ti OR adhd:ab,ti OR 'attention deficit disorder':ab,ti OR 'attention deficit disorders with hyperactivity':ab,ti OR 'attention deficit hyperactivity disorders':ab,ti OR 'attention deficit-	61,123

	hyperactivity disorder':ab,ti OR 'brain dysfunction, minimal':ab,ti OR 'minimal brain dysfunction':ab,ti	
#2	'luteolin:ab,ti OR '3,4,5,7 tetrahydroxy flavone':ab,ti OR '3,4,5,7 tetrahydroxyflavone':ab,ti OR cyticholine:ab,ti OR phosphatidylserine:ab,ti OR 'phosphatidyl serine':ab,ti OR 'phosphatidyl serines':ab,ti OR 'serine phosphoglycerides':ab,ti OR 'zizyphus honey extract':ab,ti OR 'zizyphus honey':ab,ti OR 'bacopa monnieri':ab,ti OR 'acetyl l carnitine':ab,ti OR 'acetyl carnitine':ab,ti OR (acetylcarnitine,:ab,ti AND r:ab,ti AND -isomer:ab,ti) OR alcar:ab,ti OR alc:ab,ti OR 'levocarnitine acetyl':ab,ti OR medosan:ab,ti OR magnesium:ab,ti OR zinc:ab,ti	287,110
#3	'inattention:ab,ti OR hyperactivity:ab,ti OR impulsivity:ab,ti OR 'impulsive behavior':ab,ti OR behavior:ab,ti OR qol:ab,ti OR 'quality of life':ab,ti OR 'health-related quality of life':ab,ti OR 'life quality':ab,ti	1,621,120
#4	'clinical trial':ab,ti OR 'open-label studies':ab,ti OR 'controlled clinical trial':ab,ti OR 'randomized clinical trial':ab,ti OR 'phase iii clinical trial':ab,ti	311,189
#5	#1 AND #2 AND #3 AND #4	16

Web of Science (WOS)		
Search ID#	Search terms	Results
#1	AB=(Attention Deficit Hyperactivity Disorder) OR AB=(ADHD) OR AB=(Attention Deficit Disorder) OR AB=(Attention Deficit Disorders with Hyperactivity) OR AB=(Attention Deficit Hyperactivity Disorders) OR AB=(Attention Deficit-Hyperactivity Disorder) OR AB=(Brain Dysfunction, Minimal) OR AB=(Brain Dysfunction, Minimal) OR AB=(Minimal Brain Dysfunction)	46,491
#2	AB=(Luteolin) OR AB=(3',4',5,7-Tetrahydroxy-Flavone) OR AB=(3',4',5,7-Tetrahydroxyflavone) OR AB=(Cyticholine) OR AB=(Phosphatidylserine) OR AB=(Phosphatidyl Serine) OR AB=(Phosphatidyl Serines) OR AB=(Serine Phosphoglycerides) OR AB=(Zizyphus Honey Extract) OR AB=(Zizyphus Honey) OR AB=(Bacopa Monnieri) OR AB=(Acetyl-L-Carnitine) OR AB=(Acetyl Carnitine) OR AB=(Acetylcarnitine, (R)-Isomer) OR AB=(Alcar) OR AB=(ALC) OR AB=(Levocarnitine Acetyl) OR AB=(Medosan) OR AB=(Magnesium) OR AB=(Zinc)	406,385
#3	AB=(Inattention) OR AB=(Hyperactivity) OR AB=(Impulsivity) OR AB=(Impulsive Behavior) OR AB=(Behavior) OR AB=(QoL) OR AB=(Quality of Life) OR AB=(Health-Related Quality Of Life) OR AB=(Life Quality)	3,503,928

#4	AB=(Clinical trial) OR AB=(open-label studies) OR AB=(controlled clinical trial) OR AB=(randomized clinical trial) OR AB=(phase III clinical trial)	612,034
#5	#1 AND #2 AND #3 AND #4	32

Cochrane		
Search ID#	Search terms	Results
#1	("Attention Deficit Hyperactivity Disorder" OR "ADHD" OR "Attention Deficit Disorder" OR "Attention Deficit Disorders with Hyperactivity" OR "Attention Deficit Hyperactivity Disorders" OR "Attention Deficit-Hyperactivity Disorder" OR "Brain Dysfunction, Minimal" OR "Brain Dysfunction, Minimal" OR "Minimal Brain Dysfunction"):ti,ab,kw	7,878
#2	("Luteolin" OR "3',4',5,7-Tetrahydroxy-Flavone" OR "3',4',5,7-Tetrahydroxyflavone" OR "Cyticholine" OR "Phosphatidylserine" OR "Phosphatidyl Serine" OR "Phosphatidyl Serines" OR "Serine Phosphoglycerides" OR "Zizyphus Honey Extract" OR "Zizyphus Honey" OR "Bacopa Monnieri" OR "Acetyl-L-Carnitine" OR "Acetyl Carnitine" OR "Acetylcarnitine, (R)-Isomer" OR "Alcar" OR "ALC" OR "Levocarnitine Acetyl" OR "Medosan" OR "Magnesium" OR "Zinc"):ti,ab,kw	17,974
#3	(Inattention OR Hyperactivity OR Impulsivity OR Impulsive Behavior OR Behavior OR QoL OR Quality of Life OR Health-Related Quality Of Life OR Life Quality):ti,ab,kw	327,076
#4	(Clinical trial OR open-label studies OR controlled clinical trial OR randomized clinical trial OR phase III clinical trial):ti,ab,kw	887,137
#5	#1 AND #2 AND #3 AND #4	42

JSTOR		
Search ID#	Search terms	Results
#1	((ab:"Attention Deficit Hyperactivity Disorder") OR (ab:"ADHD")) AND la:(eng OR en)	143
#2	(((((((ab:"Luteolin") OR (ab:"Cyticholine")) OR (ab:"Phosphatidylserine")) OR (ab:"Zizyphus Honey")) OR (ab:"Bacopa Monnieri")) OR (ab:"Acetyl-L-Carnitine")) OR (ab:"Magnesium")) OR (ab:" Zinc")) AND la:(eng OR en)	280

#3	(((((((ab:"Inattention") OR (ab:"Hyperactivity")) OR (ab:"Impulsivity")) OR (ab:"Impulsive Behavior")) OR (ab:"Behavior")) OR (ab:"QoL")) OR (ab:"Quality of Life")) AND la:(eng OR en)	15,296
#4	(((((ab:"Clinical trial") OR (ab:"open-label studies")) OR (ab:"controlled clinical trial")) OR (ab:"randomized clinical trial")) OR (ab:"phase III clinical trial")) AND la:(eng OR en)	741
#5	#1 AND #2 AND #3 AND #4	5

Google Scholar		
Search ID#	Search terms	Results
#1	Attention Deficit Hyperactivity Disorder OR ADHD OR Attention Deficit Disorder OR Attention Deficit Disorders with Hyperactivity OR Attention Deficit Hyperactivity Disorders OR Attention Deficit-Hyperactivity Disorder OR Brain Dysfunction, Minimal OR Minimal Brain Dysfunction	52,500
#2	Luteolin OR Cyticholine OR Phosphatidylserine OR Zizyphus Honey Extract OR Zizyphus Honey OR Bacopa Monnieri OR Acetyl-L-Carnitine OR Medosan OR Magnesium OR Zinc	10,900
#3	Inattention OR Hyperactivity OR Impulsivity OR Impulsive Behavior OR Behavior OR QoL OR Quality of Life OR Health-Related Quality Of Life OR Life Quality	901,000
#4	Clinical trial OR open-label studies OR controlled clinical trial OR randomized clinical trial OR phase III clinical trial	2,750,000
#5	#1 AND #2 AND #3 AND #4	87