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REVIEW

Attention-deficit/hyperactivity disorder and inflammation: natural product-derived treatments—a review of the last ten years

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Abstract

Objective Attention-deficit hyperactivity disorder (ADHD) is a psychiatric disorder characterized by symptoms of inattention, hyperactivity, and impulsivity. Stimulant medication is the main pharmacological treatment for ADHD. However, the traditional pharmacological treatments may have significant side effects; therefore, non-pharmacological approaches are needed. Thus, there has been growing interest in alternative herbal treatments. The aim of this review was to comprehensively assess the current evidence for plant-based treatment of ADHD in human and animal models, as well as their ability to modulate the inflammatory process.

Methods This study was an integrative review of the current evidence for the plant-based treatment of ADHD. The research involved using literature available on PubMed and Scopus databases.

Findings Spontaneously hypersensitive rats treated with baicalin exhibited significant reductions in locomotion, increased spatial learning skills, and increased levels of dopamine in the striatum. Supplementation with Sansonite improved memory and attention capacity. In human studies, *Ginkgo biloba* significantly improved the symptoms of inattention and reduced memory impairment. In studies conducted using Korean Red ginseng, Klamath, and *Crocus sativus* L., the patients showed significant improvements in symptoms of inattention and hyperactivity/impulsivity. Furthermore, we demonstrated that the identified plants modulate the inflammatory process through pro-inflammatory and anti-inflammatory cytokines, nitric oxide, Th cells, Toll-like receptor 4, and mitogen-activated protein kinases.

Conclusion All the studies included in this review focused on plants with demonstrated potential against inflammatory processes, positioning them as promising candidates for ADHD treatment, due to their potential to attenuate or even prevent neuroinflammatory mechanisms.

Keywords Attention deficit hyperactivity disorder · Inflammation · Neuroinflammation · Natural products · Plants · Animal model · Animal model for ADHD

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity (APA 2013). Epidemiological data indicate that the global prevalence of ADHD is approximately 5.3% among children aged below 18 years (Polanczyk et al. 2007). Although it initiates in childhood, it is common for symptoms to persist into adulthood, leading to social, academic, and professional impairments (Mash and Barkley 2003).

ADHD is a multifactorial disorder, and several genetic and environmental factors have already been implicated in its pathophysiology (Faraone et al. 2015). Beyond traditional neurotransmitter theories, a substantial body of

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evidence suggests a potential role for neuroinflammation in the development of ADHD. In this context, epidemiological studies have consistently revealed a significant overlap between ADHD and inflammatory and autoimmune disorders; numerous studies have evaluated serum inflammatory markers in individuals with ADHD; and genetic studies have identified polymorphisms in genes related to inflammatory pathways that may contribute to the disorder (Dunn et al. 2019; Leffa et al. 2018; Verlaet et al. 2018; Chang et al. 2021; Chen et al. 2022).

Furthermore, various environmental factors associated with heghtened inflammation, such as maternal exposure to infections (Werenberg Dreier et al. 2016), smoking during pregnancy (Silva et al. 2014; Thapar et al. 2013), maternal obesity (Andersen et al. 2018; Chen et al. 2014; Rijlaarsdam et al. 2017; Sanchez et al. 2018), and maternal exposure to toxic agents (Thapar et al. 2013) have also been linked to an increased risk of ADHD. These environmental risk factors contribute to the creation of a uterine environment characterized by elevated inflammatory activity (Shankar et al. 2011; Terasaki and Schwarz 2016), thereby supporting the theory that exposure to inflammation during developmental phases may trigger neuroinflammatory processes (Shankar et al. 2011; Terasaki and Schwarz 2016).

The primary pharmacological treatment for ADHD involves the use of central nervous system (CNS) stimulant drugs, such as methylphenidate (MPH), which increases the intrasynaptic concentrations of dopamine (DA) and norepinephrine (NE) (Faraone et al. 2015). MPH stand as a first-line drug (Fredriksen et al. 2014; Surman et al. 2013) and numerous meta analyses have consistently demonstrated its efficacy and safety (Faraone et al. 2004; Koesters et al. 2009).

However, despite the well-stablished benefits of MPH in attenuating the core symptoms of ADHD, a significant portion of patients (approximately 30%) do not experience positive responses to this treatment (Spencer et al. 1996). Moreover, reports of adverse effects, including reduced appetite and sleep disturbances, are more prevalent among children and adolescents using MPH (White et al. 2014). Additionally, it is also necessary to monitor the psychiatric status, cardiovascular function, and growth of individuals undergoing MPH treatment for potential issues such as increased blood pressure, the emergence or exacerbation of psychotic or manic disorders, the development of motor or verbal tics, and mild growth suppression (Hennissen et al. 2017; Krinzinger et al. 2019).

So, considering the complexity associated with ADHD/MPH treatment, there is a growing need for the development of new or complementary treatment approaches, especially for children (Ghuman and Ghuman 2013). In this context, there has been a growing interest in herbal medicines since numerous studies have demonstrated the therapeutic potential of natural compounds in mitigating various brain disorders (Sharifi-Rad et al. 2020; Silva et al. 2019). The beneficial effects of phytochemicals can be attributed to a range of biological mechanisms, which include antioxidant and anti-inflammatory activities (Pan et al. 2011).

However, controlled trials investigating the efficacy of herbal medicines for treating ADHD remain relatively scarce. While some natural compounds show promise, the existing body of scientific research is limited in number and sometimes exhibit methodological inadequacies (Sarris et al. 2011). Therefore, the objectives of this study were: (1) to comprehensively review the current evidence concerning the use of herbal medicines in the treatment of ADHD, both in human subjects and animal models, and (2) to compile the anti-inflammatory properties of herbal medicines already explored in the context of ADHD. If neuroinflammation plays a role in the pathogenesis of ADHD, anti-inflammatory treatments may offer a promising avenue for therapeutic exploration.

Methodology

This study is an integrative bibliographical review of the current evidence for herbal treatments to treat ADHD. The guiding question of this research was, "Which natural products and/or plants have already been used to treat patients with ADHD and/or the animal models for ADHD?"

Data were collected between June and December 2022 from the National Library of Medicine (PubMed) and Scopus databases. The search strategy used the combination of these keywords: "ADHD and natural products"; "ADHD and Plants"; "ADHD and Animal model"; "ADHD and Herbal drug"; "Natural products and Animal model for ADHD"; "Plants and Animal model for ADHD "; and "Herbal drug and Animal model for ADHD."

The inclusion criteria were as follows: (i) articles published between 2012 and 2022; (ii) research articles; and (iii) randomized clinical or experimental studies with animal models. The exclusion criteria were as follows: (i) revisions and (ii) studies that did not involve plants or products of plant origin. In addition, duplicate articles were excluded from analysis. In the data collection process, 985 articles were obtained, among which only 10 were used for this review.

The titles and abstracts of all articles obtained from the electronic search were reviewed and studies that met the inclusion criteria were obtained in an integral manner. The stages of the bibliographic research are shown in Fig. 1.

Besides, in addition to conducting a comprehensive review of the 10 selected articles, we conducted a focused search to identify studies that evaluated the anti-inflammatory effects of the identified plants.

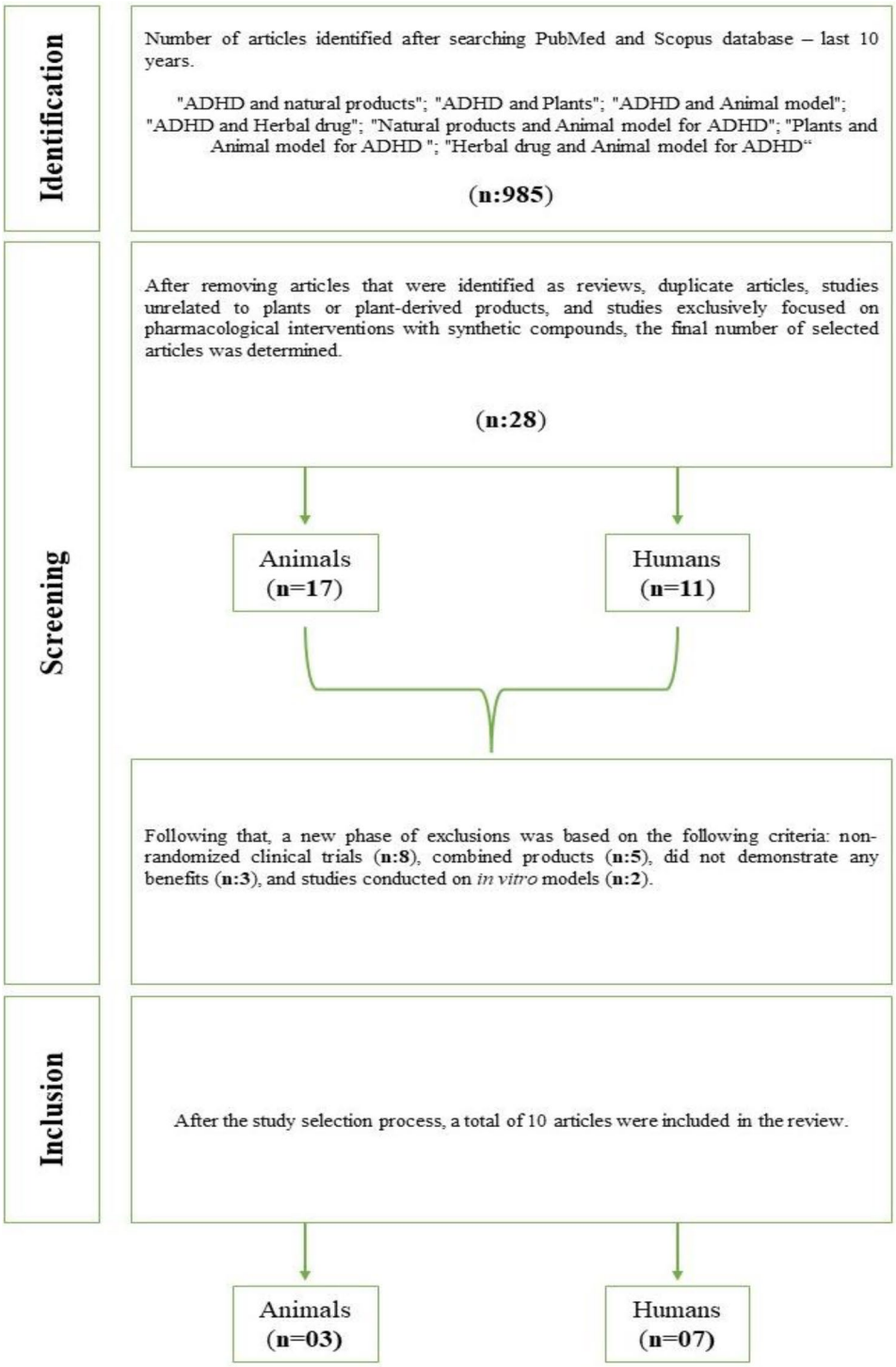

Fig. 1 Stages of bibliographic research

Results

A total of 985 research papers from literature were obtained through bibliographical research. After excluding studies that were duplicates, reviews, those that did not involve plants or products of plant origin, and those focused only on pharmacological interventions, 28 articles were selected. After the first selection, the abstracts of the selected articles were read and 18 were excluded for being non-randomized clinical trials (eight articles), combination products (six articles), no benefit (three articles), studies in in vitro models (two articles). In total, ten studies were included in the review because they met our inclusion criteria. Following a comprehensive

Table 1 Studies investigating plant alternatives for the treatment of ADHD

Plant	Composition	Study/model	Dosage	Results	References
Studies in an animal model					
Scutellaria baicalensis Georgi	Baicalin	SHR (n = 40) e WKY (n = 8)	Model group (treated with saline); methylphenidate group (MPH, 1.5 mg / kg); baicalin group (3,33 mg/mL, 6,67 mg/mL e 10 mg/mL)	After baicalin treatment, SHR rats showed significant reductions in locomotion, increased spatial learning skills	Zhou et al. (2017)
		SHR (n = 50) e WKY (n = 10)	Model group (treated with saline); methylphenidate group (MPH, 1.5 mg / kg); baicalin group (50 mg / kg); baicalin (100 mg / kg) and baicalin (150 mg / kg)	Baicalin treatment was effective in controlling the main symptoms of ADHD. Baicalin increased DA levels only in the striatum	Zhou et al. (2019)
Ziziphus jujuba Mill. var. Spinosa; Poria cocos (Schw.) Wolf;	Poria, Anemarrhenae Rhizoma and Glicirriza radix	Mice with social isolation (SI)—SI mice	Sansoninto—800 or 2400 mg/kg	After courses of treatment, mice showed marked reductions in complaints of impaired memory and attention	Fujiwara et al. (2018)
Studies with humans					
Ginkgo biloba	Flavonoid glycoside 24% and terpene lactone 6%	A randomized, double-blind, placebo-controlled clinical study. n = 66 patients	MPH—20 mg / day (10 mg / bid) < 30 kg and 30 mg / day (10 mg / t d s) > 30 kg; G. biloba—80 mg / day (40 mg / bid) < 30 kg and 120 mg / day (40 mg / tds) > 30 kg	Significant improvement was found in inattentive symptoms when G. Biloba was added to methylphenidate. In addition, it resulted in a significant increase in the overall response to clinical treatment with limited side effects	Shakibaei et al. (2015)
	EGb 761 active component of ginkgo flavonoids and lactone terpene	Randomized clinical study, controlled by control group (n = 30). n = 40 patients	240 mg daily (2 × daily) for 8 weeks	After treatment, there was clinical improvement in 24 patients (60.6%). Patients reported that they became more attentive to tasks and coped better with productive activities. After courses of treatment, patients showed marked reductions in complaints of impaired memory and attention	Chutko et al. (2019)
Pinus pinaster	Pycnogenol® -Standardized commercially available extract from the bark of French maritime pine (*Pinus pinaster*)—95% Procyanidin	A multicenter clinical trial, phase III, randomized, double-blind, controlled by placebo, and by active product. n = 144 patients	MPH ≤ 30 kg will receive 20 mg/day or ≥ 30 kg, 30 mg/day; Pycnogenol® ≤ 30 kg will receive 20 mg/day, or ≥ 30 kg, 40 mg/day	Improved total hyperactivity/impulsivity and ADHD-RS scores by Pycnogenol® compared to placebo. SEQ scores support ADHD-RS results. The Pycnogenol® group reported fewer adverse effects compared to the MPH group	Verlaet et al. (2017) Weyns et al. (2022)

Table 1 (continued)

Plant	Composition	Study/model	Dosage	Results	References
Bacopa Monnieri	Extract of *Bacopa monnieri* standardized to contain not less than 55% bacosides (CDRI 08®)	A randomized, double-blind, placebo-controlled clinical trial. n = 120 patients	Bacopa (1 × 160 mg) or placebo (if between 20 and 35 kg); Bacopa (2 × 160 mg) or placebo (if over 35 kg) per day for 14 weeks	CDRI 08® did not show significant behavioral improvements between treatment groups. The best results were cognitive as: decreased occurrence of errors, improvements in cognitive flexibility, executive functioning, interpersonal problems and sleep routine were observed in those who consumed CDRI 08® instead of placebo. The CDRI 08® did not show good behavioral results, but it can bring cognitive, mood and sleep benefits in children aged 6 to 14 years	Kean et al. (2015) Kean et al. (2022)
Panax ginseng	Ginsenosides, polyacetylene, acid polysaccharides, antioxidant aromatics, and insulin-like acid peptides	A randomized, placebo-controlled, double-blind study. n = 70 patients	Ginseng—40 mL of red ginseng extract (1 g of concentrated extract) or placebo—40 mL	Compared with placebo, ginseng extract significantly improved symptoms of inattention and hyperactivity/impulsivity	Ko et al. (2014)
Klamath	Beta-PEA, Phycocyanins AFA, and mycosporin type amino acids from 0.8% to 1% of the dry extract	A randomized clinical study. n = 30 patients	Klamin—< 25 kg-125 mg in the first month and 250 mg from the second to the sixth month; > 25 kg—300—600; > 40—600—1200	After 6 months of therapy, patients showed significant improvements based on assessments of their general functioning, behavioral aspects related to inattention and hyperactivity-impulsivity. At the end of the study, more than 50% of individuals (13 families) chose to continue treatment with Klamin	Cremonte et al. (2017)
Crocus sativus L	Crocetin, crocin, picrocrocina and safranal	A randomized, double-blind study for 6 weeks. n = 54 patients	MPH—week 1: 10 mg / d (5 mg in the morning and 5 mg at noon); week 2: 20 mg / d (10 mg in the morning and 10 mg at noon) and week 3: 20 mg / d < 30 kg and 30 mg / d for children > 30 kg. Crocus Sativus—20 to 30 mg / d (20 mg / d for < 30 kg and 30 mg / d for > 30 kg)	Short-term turmeric capsule therapy has shown the same efficacy compared to methylphenidate. However, more extensive controlled studies, with longer treatment periods, are needed for future studies	Baziar et al. (2019)

ADHD, Attention-Deficit/Hyperactivity Disorder; SHR, Spontaneously Hypertensive Rat; WKY, Wistar Kyoto; DA, Dopamine; MPH, methylphenidate; SI, social isolation

review of the 10 articles (Table 1), we subsequently focused on a total of 8 plant species for which we identified the more recent original articles that illustrate their impacts on inflammatory processes (Table 2).

Moving forward, we will present the studies and their respective plants investigated in the past decade for the treatment of ADHD, highlighting how these plants act to modulate the inflammatory process.

Interventions herbs

Bacopa monnieri

Bacopa monnieri (BM), belonging to the family *Scrophulariaceae*, is a creeping herb growing in wet and swampy areas in the Indian subcontinent. *Bacopa* has been used for approximately 3000 years in ayurvedic medicine to improve memory and intellect (Gohil and Patel 2010). In addition to modulating the monoaminergic system, BM improves

Table 2 Anti-inflammatory activity of the investigated plants for the treatment of ADHD

Plant	Anti-inflammatory activity	References
Bacopa Monnieri	↓TNF α, ↓IL-6, ↓IL-1β ↓Caspase-1, ↓Caspase-3 ↓MMP-3, ↓MCP-1 ↓COX-2, ↓NO, ↓iNOS	Nemetchek et al. (2017) Saini et al. (2019) Abhishek et al. (2022)
Crocus sativus L	↑IL-10, ↓IL-6, ↓TNF-α ↓NF-κB p65 ↓p-NF-κB p65	Abbaszade-Cheragheali et al. (2022) Akbari-Fakhrabadi et al. (2019) Xu et al. (2022)
Ginkgo Biloba	↑ $CD3^+$, $CD4^+$ ↑IL-1*β*, ↓IL-1α, ↓IL-6, ↓TNF-α ↑IL-37, ↑IL-38 ↓NF-κB p65, ↓p-NF-κB p65 ↓CXCL 10 (IP-10) ↓p-JAK2, ↓p-STAT3	Zhang et al. (2022) Mohammed et al. (2020) Zhang et al. (2018)
Klamin®	↓p-NF *κ* B ↓IL 1*β*, ↓*IL 6*	Nuzzo et al. (2018)
Panax ginseng	↑IL-10, ↓IL-6, ↓TNF-α ↓NO ↓p-NF *κ* B ↓p-JNK, ↓p-ERK-1/2, ↓p-p38	Cheah et al. (2022) Yang et al. (2022) Kumar et al. (2014)
Scutellaria baicalensis	↓*IL-1*β ↓*IL-18* ↓TLR4 ↓Caspase-1, ↓Caspase-3 ↓COX-2 ↓iNOS, ↓NO ↓TLR4, ↓IRAK4, ↓IRAK1 ↓*p-NF* κ *B* p65, ↓NF-κB p105 ↓p-JNK, ↓p-ERK, ↓p-p38, ↑p-IκB*α*	Jin et al. (2019) Li et al. (2022) Wang et al. (2022)
Ziziphus jujuba	↓TNF- *α,* ↓*IL-6* ↓*INF- γ* ↓NO, ↓iNOS ↓COX-2	Kandeda et al. (2021) Tran et al. (2019)
Pinus pinaster	↓*IL-1*β, ↓TNF-α ↓p-IκB-α ↓NO, ↓iNOS ↓COX-2	Lee et al. (2023) Go et al. (2022) Jeong et al. (2022)

CD3+, Cluster of Differentiation 3 positive; CD4+, Cluster of Differentiation 4 positive; COX-2, Cyclooxygenase-2; CXCL 10 (IP-10), C-X-C Motif Chemokine Ligand 10 (Interferon-gamma inducible protein 10); IL-1α, Interleukin-1 alpha; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; IL-10, Interleukin-10; IL-18, Interleukin-18; IL-37, Interleukin-37; IL-38, Interleukin-38; INF-γ, Interferon-gamma; iNOS, Inducible Nitric Oxide Synthase; IRAK1, Interleukin-1 Receptor-Associated Kinase 1; IRAK4, Interleukin-1 Receptor-Associated Kinase 4; p-IκBα, Phosphorylated IκBα protein; MCP-1, Monocyte Chemoattractant Protein-1; MMP-3, Matrix Metalloproteinase-3; NF-κB p65, Nuclear Factor-kappa B subunit p65; p-NF-κB p65, Phosphorylated Nuclear Factor-kappa B subunit p65; NF-κB p105, Nuclear Factor-kappa B subunit p105; NO2, Nitrogen Dioxide; p-ERK-1/2, Phosphorylated Extracellular Signal-Regulated Kinase ½; p-JAK2, Phosphorylated Janus Kinase 2; p-JNK, Phosphorylated c-Jun N-terminal Kinase; p-NF κ B, Phosphorylated Nuclear Factor-kappa B; p-p38, Phosphorylated p38 Kinase; p-STAT3, Phosphorylated Signal Transducer and Activator of Transcription 3; TNF α, Tumor Necrosis Factor alpha; TLR4, Toll-like Receptor 4

oxidative status, thus protecting the nervous system from oxidative stress and neuronal cell death (Shinomol et al. 2012; Sheikh et al. 2007) and displaying adaptogenic properties (Sheikh et al. 2007). Bacopa is currently recognized for its potential effects in the treatment of mental illnesses and epilepsy (Dhawan and Singh 1996). Several phytochemical studies have shown that BM contains numerous active constituents, including alkaloids, betulin acid, stigmasterols, saponins, and sitosterols; however, the primary components are steroidal saponins and bacosides A and B (Chatterji et al. 1965).

Dave et al. (2014) investigated the effectiveness of the BM extract on ADHD symptoms in children. This open-label clinical trial included 31 children aged 6–12 years diagnosed with ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The intervention included a 225 mg/day dose of BM extract administered for 6 months. The Parent Rating Scale was used to assess the baseline and end-of-study ADHD symptom scores. Treatment with BM for 6 weeks significantly reduced the subtest scores for ADHD symptoms, except for social problems. Symptom scores for restlessness and self-control reduced, along with improvement in attention deficit symptoms, learning problems, impulsivity, and psychiatric problems (Dave et al. 2014). The authors concluded that the standardized BM extract was effective in controlling ADHD symptoms and was well-tolerated by children. Randomized, double-blind, placebo-controlled clinical trials are currently underway (Kean et al. 2015). Kean et al. (2022) presented the first results of their study on BM for the treatment of children diagnosed with ADHD. Treatment with BM (CDRI 08 standardized to 55% bacosides) was administered for 14 weeks at the following doses: 1 × 160 mg CDRI 08, 2 × 160 mg CDRI 08, or placebo per day. After 14 weeks, no improvement in ADHD symptoms was observed; however, processing speed and cognitive flexibility improved, along with an improvement in mood and sleep quality (Kean et al. 2022). Thus, researchers claim that limitations with dropouts and external factors, such as physical exercise, may have altered the study outcomes and thus necessitated further studies.

Bacopa monnieri—inflammatory processes

Saini et al. (2019) aimed to assess whether BM prevented colchicine-induced inflammation and Aβ production. To demonstrate the effect, Wistar rats were induced into dementia through a single intracerebroventricular injection of colchicine (15 µg/5 µl), while BM extract was orally administered (50 mg/kg body weight, daily) for 15 days. A significant increase in pronounced nitric oxide (NO) production was observed, along with an elevation in the expression of cytokines IL-6, TNF-α, and chemokine MCP-1, as well as COX-2 and iNOS expression induced by colchicine. On the other hand, BM supplementation was able to attenuate all inflammatory markers in the animals' brain regions. Nemetchek et al. (2017) investigated BM's ability to inhibit the release of pro-inflammatory cytokines from the murine microglial cell lineage N9, originally derived from CBA mice. Multiple BM extracts were prepared and tested to determine whether they inhibited TNF-α and IL-6 release, as well as acted as inhibitors of caspase-1 and matrix metalloproteinase-3 (enzymes associated with inflammation), and caspase-3. Findings showed that different preparations, including tea infusions, alkaloid extracts of bacopa, as well as Bacoside A, significantly inhibited the release of TNF-α and IL-6, and effectively inhibited caspases 1 and 3, along with matrix metalloproteinase-3, in the cell-free assay. Lastly, Abhishek et al. (2022) assessed the neuroprotective effect of BM in an experimental model of autism spectrum disorder (ASD) in Wistar rats and explored its mechanism of action. For this, acid was administered at a dose of 600 mg/kg to mimic the ASD model. BM was tested at concentrations of 20, 40, and 80 mg/kg, and inflammatory cytokines IL-1β, IL-6, IL-10, TNF-α were evaluated. The results indicated that BM exhibits anti-inflammatory properties (at a concentration of 80 mg/kg), reducing IL-1β, IL-6, TNF-α levels.

Scutellariae baicalensis

For more than 2000 years, the root of *Scutellariae baicalensis* has been used in East Asia for therapeutic purposes, to treat diarrhea, vomiting, menstrual complications, hepatitis, diabetes, and hypertension. The main bioactive compound of the plant is baicalin, obtained from its dried root (Shang et al. 2010). Furthermore, it has been used as an anti-allergic, anti-inflammatory, and antibacterial agent to treat inflammatory and allergic diseases (Sun et al. 2013).

Several in vivo and in vitro studies have analyzed the potential protective effects of baicalin against oxidative injuries (Yin et al. 2011), improvements in memory impairment (Chen et al. 2015), and learning (Xiong et al. 2014). Another study using baicalin showed a significant increase in the gene and protein expression levels of antioxidant enzymes (Ding et al. 2015). Due to these potential effects, some studies have analyzed baicalin and substantiated its potential in treating the primary symptoms of ADHD.

Zhou et al. (2017) evaluated the effect of baicalin treatment in vivo (spontaneously hypersensitive rats [SHR] and Wistar Kyoto models for ADHD) at three concentrations (3.33, 6.67, and 10 mg/mL) twice daily for 4 weeks. Hyperactivity and impulsivity were evaluated using the open-field test and Morris Water Maze. Eventually, they concluded that both baicalin and MPH, which are being used for the treatment of ADHD, can normalize the exercise capacity and

learning and memory capacity of SHR, thus controlling the main symptoms of hyperactivity, impulsivity, and inattention from ADHD (Zhou et al. 2017). Moreover, the efficacy of baicalin was dose-dependent, with high doses having the greatest effect on the evaluated parameters. To elucidate the potential mechanism of action of baicalin after testing its therapeutic effects on ADHD in an animal model (SHR and Wistar Kyoto), Zhou et al. (2019) used the theory of dopamine deficit. In this study, SHR were divided into the following five groups: MPH, baicalin (50, 100, or 150 mg/kg), and saline-treated controls. Motor activity, spatial learning, and memory capacity were assessed using the open-field and Morris water maze tests. To elucidate the mechanism of action, the sinaptossomal mRNA and protein expressions of tyrosine hydroxylase (TH), vesicular monoamine transporter 2 (VMAT2), 25 kD molecular mass synaptosome-associated protein (SNAP25), and syntaxin 1a were evaluated. Finally, dopamine levels in the prefrontal cortex (PFC) and striatum were assessed. The results indicated that both MPH and baicalin at doses of 150 mg/kg and 100 mg/kg significantly decreased hyperactivity, improved spatial learning and memory deficits, and increased sinaptossomal mRNA and protein levels of TH, SNAP25, VMAT2, and syntaxin 1a, compared with saline treatment. MPH significantly increased the DA levels in the PFC and striatum, whereas baicalin significantly increased the DA levels in the striatum. Finally, the researchers suggested that baicalin may target the striatum and that the increased levels of DA may be partially attributed to the increased mRNA and protein expression of TH, SNAP25, VMAT2, and syntaxin 1a (Zhou et al. 2019).

Scutellariae baicalensis—inflammatory processes

Jin et al. (2019) aimed to investigate the effects of pre-treatment with baicalin on neuronal protection against microglia-induced neuroinflammation. They used the transgenic mouse model APP (amyloid beta precursor protein)/PS1 (presenilin-1). Baicalin was administered via intragastric route at a dose of 103 mg/kg. The results indicated that baicalin decreased the production of IL-18 and IL-1β proteins, as well as mRNA levels of IL-1β, IL-18, and iNOS. They also observed a reduction in caspase-1 and caspase-3, attenuating cell death, and appeared to inhibit the TLR4/NF-κB signaling pathway. Li et al. (2022) assessed the modulatory effect of baicalin on neuroinflammation in lipopolysaccharide (LPS)-activated BV-2 cells. Cells were treated with baicalin at concentrations of 2.5, 7.5, and 22.5 μM. Results showed that higher concentrations of baicalin led to a decrease in inflammatory mediators such as NO, iNOS, IL-1β, and COX-2. Baicalin also appeared to regulate proteins related to the Toll-like receptor 4 (TLR4)/myeloid differentiation factor 88 (MyD88)/nuclear factor κB (NF-κB) pathway and suppressed the phosphorylation of mitogen-activated protein kinase family proteins (JNK, ERK, and p38). Lastly, Wang et al. (2022) demonstrated the effect of *Scutellaria baicalensis* in treating psoriasis using an animal model. They utilized Balb/c mice and induced psoriasis with an imiquimod (IMQ) cream. To evaluate the effect of *Scutellaria baicalensis*, the skin was treated with a dose of 1 g/kg for 5 days, resulting in improvement in evaluated skin parameters. For inflammation assessment, macrophages (RAW264.7 cells) were used, and inflammation was induced by LPS. Cells were treated with baicalin at concentrations of 156 and 625 μg/mL. The results showed a decrease in COX-2, iNOS, NO expression, as well as NF-κB p65 and NF-κB p105.

Crocus sativus L.

Crocus sativus L., also known as saffron, is a perennial herb widely grown in India, Greece, and Iran. The oldest reference for its cultivation is in 2300 BC, and its consumption has increased significantly since then. Saffron is used in traditional Indian medicine as an analgesic and cardioprotective agent for various types of mental illnesses (Alonso et al. 2012). Moreover, turmeric and its constituents inhibit DA and NE reception (Pitsikas and Sakellaridis 2006; Pitsikas et al. 2008).

Two in vivo experiments using saffron extract indicated that its administration was useful in treating neurodegenerative disorders and memory impairment, with significant improvements in learning and memory skills (Abe and Saito 2000; Sugiura et al. 1995). Baziar et al. (2019) compared the safety and effectiveness of saffron and MPH in improving ADHD symptoms in children. This was a 6-week, double-blind randomized trial, including 54 children aged 6–17 years, diagnosed with ADHD, according to DSM-IV. These children randomly received treatment with MPH or saffron capsules, depending on their weight (20 mg/d for < 30 kg and 30 mg/d for > 30 kg). Symptoms were assessed using the Attention-Deficit/Hyperactivity Disorder Rating Scale IV for Teachers and Parents (ADHD-RS-IV) at baseline, 3 weeks, and 6 weeks. The authors found no significant difference in ADHD-RS-IV scores between the two groups at baseline and the end of the study ($p = 0.731$ and $p = 0.883$, respectively). The frequencies of adverse effects were similar between the saffron and MPH groups. Thus, the authors concluded that short-term therapy with saffron was as effective as that with MPH. However, larger controlled studies with longer treatment periods are warranted (Baziar et al. 2019).

Blasco-Fontecilla et al. (2022) compared the efficacy of saffron and MPH in children and young adults diagnosed with ADHD. The study was characterized as prospective, naturalistic, non-randomized, and non-blinded, where 56 patients aged 7–17 years were divided into the following two groups: the saffron group receiving psychoeducation

and saffron (30 mg/day) and the MPH group receiving extended-release MPH (1 mg/kg per day) for 3 months. To assess the symptoms of hyperactivity and inattention, the following scales were used: SNAP-IV and the revised Conners Parental Rating Scale, to assess executive functions; the Behavioral Rating Inventory of Executive Function—Second Edition, to assess impulsivity; Conners' Continuous Performance Test, version 3, to assess sustained attention; and Sleep Disturbances Scale for Children, to assess sleep quality. The key finding here was that the efficacy of saffron is comparable to that of MPH. Saffron is the most effective in treating the symptoms of hyperactivity, while MPH is the most effective in treating the symptoms of inattention; both treatments are well-tolerated and no significant side effects have been reported. Finally, saffron markedly improves the time taken to fall asleep, according to the parents' reports. Thus, the study verified the effectiveness and safety of saffron extract compared to those of MPH. This, along with other studies, confirmed that saffron is a potential candidate for the treatment of ADHD (Blasco-Fontecilla et al. 2022).

Crocus sativus L.—inflammatory processes

Abbaszade-Cheragheali et al. (2022) assessed the effects of crocin, a constituent of saffron, on anxiety and depression induced by unpredictable chronic mild stress (UCMS) in rats. The rats underwent UCMS and were treated with crocin (10, 20, and 30 mg/kg) for 4 weeks. Inflammatory parameters and oxidative stress damage were evaluated afterward. The authors demonstrated that UCMS altered the assessed parameters, and crocin at concentrations of 20 and 30 mg/kg reduced serum corticosterone levels, malondialdehyde (MDA), TNF-α, and IL-6, while increasing IL-10 and brain-derived neurotrophic factor (BDNF) levels in cortical tissues. Akbari-Fakhrabadi et al. (2019) evaluated the effect of saffron treatment on resistance capacity, mitochondrial biogenesis, inflammation, antioxidants, and metabolic biomarkers in Wistar rats subjected to resistance training. The rats underwent resistance training and received saffron at a concentration of 40 mg/kg. IL-6 levels were assessed, and decreases in IL-6 levels were observed, alongside improvements in other parameters such as malondialdehyde, CPK, and AST. These findings indicated that saffron increased mitochondrial biogenesis, reduced oxidative stress and inflammation, and modulated metabolic biomarkers. Xu et al. (2022) evaluated the effect of crocin on breast cancer cells. They assessed the levels of nuclear factor kappa B (NF-κB) p-p65 and p65, as well as TNF-α and IL-1β levels. The results demonstrated that crocin inhibited NF-κB activation, suppressed cell viability and proliferation in breast cancer cells (BC). Crocin significantly reduced TNF-α and IL-1β levels, suggesting its role in suppressing inflammation in BC cells.

Ginkgo biloba

Ginkgo biloba (*Ginkgoaceae*), a plant native to China, has been used in traditional Chinese medicine for centuries. It is classified as one of the oldest seed plants, owing to which, it is usually called the "living fossil". Moreover, this tree can live for over a thousand years, reaching up to forty meters in height. The leaf and seed extracts have been used for several years to treat circulatory disorders, asthma, vertigo, and cognitive problems (Kleijnen and Knipschild 1992).

These therapeutic effects are attributed to their active ingredients, including terpenoids, flavonol glycosides, and proanthocyanidins, among which flavonol glycosides are the most prevalent (Kleijnen and Knipschild 1992; Pang et al. 1996). Several clinical studies have evaluated the efficacy of *G. biloba*. In addition, studies in an animal model have revealed that this plant increases central dopaminergic activity (Yeh et al. 2011).

Shakibaei et al. (2015) evaluated the effectiveness of *G. biloba* as a complementary therapy for children and adolescents with ADHD. This clinical trial was randomized, double-blind, placebo-controlled, and registered (registration number: IRCT2014111519958N1). This study included 60 patients receiving MPH (20–30 mg/day) and *G. biloba* (80–120 mg/day) or placebo for 6 weeks. The following two rating scales were used: the ADHD Rating Scale-IV (ADHD-RS-IV), parent and teacher ratings (days 1, 2, and 6), and the Children's Global Assessment Scale (days 1 and 6). Importantly, compared to the placebo, *G. biloba* reduced the ADHD-RS-IV parent inattentiveness score, total score, and the teacher inattentiveness score. The response rate was higher with *G. biloba* than that with the placebo, based on parental assessment. Therefore, the authors identified *G. biloba* as an effective complementary treatment for ADHD; however, additional studies with a longer duration of treatment are necessary (Shakibaei et al. 2015).

Another randomized clinical study was conducted by Chutko et al. (2019), whose objective was to evaluate the effectiveness of a memoplant formulation (EGb 761, a standardized *G. biloba* leaf extract) in the treatment of adult patients diagnosed with ADHD. Here, 40 patients aged 18–45 years diagnosed with ADHD and 30 healthy adults were evaluated as controls. Memoplant was administered at a dose of 240 mg once daily for 8 weeks. Clinical, psychological, and electroencephalographic (EEG) tests were also performed. The results showed that adult patients with ADHD had subjective and objective impairments in memory and attention; the EEG suggested dysfunction of the frontothalamic regulatory system and a deficit of nonspecific activation by the reticular system. Twenty-four (60%) patients administered memoplant showed general clinical improvements, followed by reduced attention deficit and improved measures of memory (Chutko et al. 2019). In summary, *G.*

biloba can be perceived as a potential candidate for ADHD treatment.

Ginkgo biloba—inflammatory processes

Zhang et al. (2022) aimed to evaluate the effect of Ginkgo Biloba extract (GBE) on cardiac and cerebral inflammation in rats subjected to a high-fat diet (HFD) combined with unpredictable chronic mild stress (UCMS). The animals received 40 mg/kg/day of GBE for 8 weeks. They assessed helper T lymphocytes (CD3 + , CD4 +) and interleukins (IL-) 1β, IL-37, IL-38. They also evaluated nuclear factor kappa B (NF-κB) p65 and p-p65. The results showed that rats exposed to HFD + UCMS and treated with GBE exhibited elevated levels of helper T lymphocytes and serum anti-inflammatory cytokines including IL-37 and IL-38. Additionally, GBE inhibited the canonical NF-κB signaling pathway through negative regulation of p-p65 expressions. Mohammed et al. (2020) demonstrated the neuroprotective effect of GBE in a rotenone-induced Parkinson's Disease model in animals. The animals were treated with GBE (150 mg/kg/day) for 20 days, followed by a combination with rotenone (2.5 mg/kg/day) for 50 days. Inflammatory profile was assessed through IL-1β, IL-6, and TNF-α. The results showed that GBE treatment reduced the levels of IL-1β, IL-6, and TNF-α. Finally, Zhang et al. (2018) revealed the neuroprotective and anti-inflammatory effects of GBE extract in in vitro and in vivo models of cerebral ischemia. They used doses of 7.5 and 15 mg/kg of GBE extract. The results indicated that GBE significantly attenuated cerebral infarction and neuronal apoptosis. It also reduced the levels of inflammatory cytokines IL-1α, IL-6, and CXCL10 (IP-10), inhibited astrocyte activation, and decreased the phosphorylation of STAT3 and JAK2.

Panax ginseng

Red Ginseng (*Panax ginseng*) is considered as the most popular herbal medicine used globally. It has several positive effects on glucose metabolism, psychomotor function, and lung disease. Korean Red Ginseng (KRG) contains ginsenosides, polyacetylenes, acidic polysaccharides, aromatic compounds, antioxidants, and acidic peptides.Among these, ginsenoside has potent effects, as an anti-inflammatory, anticarcinogenic, and anti-stress agent, along with potent effects in the central nervous system (Christensen 2008).

Clinical studies have evaluated the potential positive effects of KRG on fatigue, insomnia, and depression (Tode et al. 1999). Some studies have also investigated the effects of KRG on ADHD symptoms. Ko et al. (2014) conducted a double-blind, placebo-controlled, randomized clinical trial to evaluate the effects of KRG on children with ADHD symptoms. Seventy patients aged 6–15 years were divided in the KRG (n = 33) and control (n = 37) groups. The KRG group received a pouch of KRG (1 g KRG extract/bag) twice daily, whereas the control group received a pouch of placebo twice daily for 8 weeks. The DSM-IV criteria were used to evaluate the inattention and hyperactivity scales. Secondary outcomes were quantitative EEG theta/beta ratio (QEEG TBR), and salivary cortisol and dehydroepiandrosterone (DHEA) levels. No differences were observed in the baseline characteristics between the KRG and control groups. After 8 weeks, the KRG group showed significantly lower inattention/hyperactivity scores than those of the control group. Moreover, the KRG group showed a significantly lower QEEG TBR than that in the control group. However, there were no significant differences in salivary cortisol or DHEA levels at week 8 compared with the baseline levels. No serious adverse events were reported in any of the groups. The authors concluded that KRG treatment may be an effective and safe alternative for children with symptoms of inattention and hyperactivity/impulsivity. However, further studies are required to corroborate these findings (Ko et al. 2014).

Panax ginseng—inflammatory processes

Cheah et al. (2022) evaluated the in vitro anti-neuroinflammatory properties of Panax ginseng root extract based on NO and cytokine production. BV2 microglial cell culture stimulated with lipopolysaccharides was treated with the extract, and its anti-neuroinflammatory properties were assessed by measuring NO production, as well as TNF-α, IL-6, and IL-10 levels. In this study, the authors did not observe differences in NO, TNF-α, and IL-6. However, Panax ginseng extract significantly increased interleukin IL-10 compared to untreated cells. Kumar et al. (2014) demonstrated in their animal model of cerebral trauma that Panax ginseng (100 and 200 mg/kg) for 2 weeks significantly attenuated neuroinflammatory changes measured by TNF-α and IL-6. Yang et al. (2022) showed in their study the effect of ginseng extract on inflammation and oxidative stress in RAW264.7 cells and in an animal model with dextran sulfate-induced colitis (DSS). Their results showed that ginseng extract reduced levels of nitric oxide, TNF-α, and IL-6 secreted by LPS-treated cells. The treatment inhibited NF-κB activity and the phosphorylation of JNK, ERK-1/2, and p38.

Klamin®

Recently, microalgae from Lake Klamath have been studied for their potential effects on attention, mood, and anxiety. The extracts of these algae can reduce mood changes, such as anxiety and depression, and improve learning (Genazzani et al. 2010; Sedriep et al. 2011). These microalgal extracts contain different compounds, such as phenylethylamine

(PEA), mycosporin-type amino acids (MAAs), AFA-phycocyanins, and AFA-phytochrome, which could be involved in related responses. Recently, Klamath microalgae extract was patented (Klamin®: β-phenylethylamine-12 mg/g AFA-phycocyanins-10%), MAAs-2%), and AFA-phytochrome (1%) were produced by the Center Research in Nutrition, Urbino, Italy) (Benedetti et al. 2004).

One study has been conducted in humans in the last decade. Cremonte et al. (2017) used Klamin® to treat the main ADHD symptoms. This study included 25 patients, aged 6–15 years diagnosed with ADHD according to the DSM-IV criteria. Supplementation was administered to all the participants for 6 months (in liquid or tablet form), according to their weight (125–1200 mg/kg). All patients were evaluated at baseline and at the end of the 6-month period. The following scales were used: inattention and hyperactivity-impulsivity, Child Global Rating Scale; SNAP IV (Conners-R Parent Rating Scale); oppositional defiant disorders (ODD subscale, SNAP IV); attention functions (Bell Test); executive functions (Tower of London test); freedom from distraction parameter (LD, Wechsler Intelligence Scale for Children III [WISC III scale]); short-term verbal memory (of numbers, WISC III scale); and arithmetic reasoning and mental math skills (arithmetic reasoning, WISC III scale). As main results, the authors showed that the use of Klamin® provided significant improvements based on assessments of its general functioning, behaviors related to inattention and hyperactivity-impulsivity, attention functions in the selective and sustained component, and executive functions. Finally, they proved the initial hypothesis that Klamin® extract improves ADHD symptoms; however, additional studies with a larger sample size are necessary (Cremonte et al. 2017).

Klamin®—inflammatory processes

Nuzzo et al. (2018) aimed to demonstrate the antioxidant and neuroprotective effects of AFA extract Klamin® in a LAN5 neuronal cell model. Following cellular cytotoxicity experiments, a dose of 800 ng/µl was employed to assess the inflammatory profile through interleukins (IL-1β and IL-6) and p-NFκB. The results indicated that the AFA extract reduced the levels of IL-1β and IL-6, and inhibited p-NFκB, suggesting a positive role in alleviating neuroinflammation.

Pinus pinaster

Pinus pinaster belongs to the *Pinaceae* family; it is mainly found in the western Mediterranean region and can live for up to 300 years. The pine tree has been cultivated in vast monocultures in southern France, and since the middle ages, its preparations have been used for wound healing and treating scurvy (Chandler et al. 1979). The outer bark, which is relatively redder, is used for Pycnogenol® extraction. Pycnogenol® is a patented (Horphag Research), commercially available extract of French maritime pine bark. Some known properties of Pycnogenol® include anti-inflammatory activity, radical scavenging activity, and reduction of menstrual cramps and pain.

Pycnogenol is mainly composed of phenolic compounds, glycosides, glucose esters, procyanidins, and flavonoids (Packer et al. 1999). In addition to its extract being marketed for clinical purposes, it can also be used as a supplement, ingredient in cosmetics, and food additive (Rohdewald 2004). However, owing to its antioxidant and immunomodulatory properties, clinical studies have been conducted with Pycnogenol® in children and adolescents with ADHD, and favorable results have been obtained.

Trebatická et al. (2006) evaluated the effects of the Pycnogenol® extract in a randomized, placebo-controlled clinical study and showed that Pycnogenol® administration significantly reduces hyperactivity and improves attention, concentration, and visual-motor coordination (Trebatická et al. 2006). Based on these findings, Verlaet et al. (2017) presented a Phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial (Clinicaltrials.gov number: NCT02700685; EudraCT 2016-000215-32) to evaluate the effect of Pycnogenol® treatment in ADHD. This study included 144 patients (aged 6–12 years), divided into the following three groups: MPH: patients with body weight < 30 kg administered at 20 mg/day, ≥ 30 kg at 30 mg/day. Treatment during the first week always contains 10 mg, increasing by 10 mg each week to limit side effects; Pycnogenol®: patients with body weight < 30 kg will receive 20 mg/day, those with body weight ≥ 30 kg, 40 mg/day, targeting a daily dose of 1 mg/kg. Treatment for the first 2 weeks was maintained at 20 mg; the placebo contained excipients only. Different analytical tools, such as (*ADHD-RS* ADHD-Rating Scale), Social-Emotional Questionnaire (SEQ), Physical Complaints Questionnaire, Food Frequency Questionnaire, erythrocyte glutathione analysis, and lipid-soluble antioxidant analysis. Antioxidant enzyme activity, plasma malondialdehyde, *8-OHdG* 8-hydroxy-2-deoxyguanosine, cytokine, antibody, peripheral blood mononuclear cell count and reactivity, microbial composition, catecholamine, serum neuropeptide Y, zinc, and genetic analyses, were used for evaluation. All measurements were performed at baseline, and after 5 and 10 weeks of treatment (Verlaet et al. 2017). Weyns et al. (2022) reported that 88 patients completed the protocol. Teachers reported significant improvement in total and ADHD-RS hyperactivity/impulsivity scores using Pycnogenol® and MPH after 10 weeks, compared to those in the placebo. The SEQ scores corroborated the ADHD-RS results. Adverse effects were reported five times more frequently for MPH than those for Pycnogenol®. This is an ongoing study, however, the available results show promising perspectives regarding the use

of Pycnogenol® for the treatment of ADHD (Weyns et al. 2022).

Pinus pinaster—inflammatory processes

Lee et al. (2023) investigated the neuroprotective effects of Pinus pinaster and its therapeutic mechanisms in an animal model of cerebral ischemia. Rats underwent common carotid artery occlusion and were then treated with Pycnogenol (25, 50, and 100 mg/kg, respectively) immediately, 24 h, and 48 h after occlusion. Immunohistochemistry for interleukin-1β (IL-1β) was performed to assess the inflammatory profile. Results showed that in addition to attenuating ischemic injury, only the dose of 100 mg/kg inhibited IL-1β expression, thereby reducing inflammation. Go et al. (2022) studied the effect of Pinus pinaster extract against cognitive decline and neuroinflammation caused by Alzheimer's Disease (AD) in an animal model induced by intracerebral Aβ 1–42 injection. The animals were treated with the extract orally at concentrations of 15 and 30 mg/kg. To assess the neuroinflammatory profile, levels of TNF-α, p-JNK, p-IκB-α, COX-2, and IL-1β expression were measured. The results showed a decrease in TNF-α, p-IκB-α, and IL-1β levels in animals treated with the extract at the concentration of 30 mg/kg. Jeong et al. (2022) investigated the antioxidant and anti-inflammatory effects of ethanolic extract of Pinus pinaster in vitro and in vivo under acute inflammation conditions. Here, we will report the in vitro experiments, where inflammatory mediators (NO, iNOS, COX-2, TNF-α, and IL-1β) were assessed in LPS-stimulated RAW264.7 cells treated with different concentrations of pinus extract (6.25, 12.5, 25, 50, and 100 µg/mL). The authors showed that pinus extract at concentrations of 25 and 100 µg/mL significantly reduced levels of NO, iNOS, COX-2, TNF-α, and IL-1β.

Ziziphus jujuba Mill. var. *spinosa*

Ziziphus jujuba Mill. var. *spinosa* is a thorny and branched deciduous plant of the *Rhamnaceae* family, which is widely distributed in northern and northeastern China. It has been used as an analgesic, tranquilizer, and anticonvulsant for over 2500 years in countries such as China and Korea. These effects are attributed to pharmacologically active compounds, such as flavones, alkaloids, and triterpenes (Cheng et al. 2000). Sansoninto (SST), a traditional herbal medicine used in Japan, China, and Taiwan, is extracted from its dried seeds and has positive effects on insomnia, depression, and neuropathy (Saito et al. 2000).

Because of the beneficial constituents of SST, some studies have assessed their effects on the main ADHD symptoms. Fujiwara et al. (2018) analyzed the potential of SST in the treatment of behavioral symptoms and neurochemical parameters in an animal model of ADHD. The study included 44 male mice (4-week-old), divided into the following four groups (n = 11 each): control (water), socially isolated (water), SST 800 mg/kg, or SST 2400 mg/kg. SST or water was orally administered once daily. Sociability, water seeking, and fear conditioning tests were performed at 9, 10, and 11 weeks of age. After completing the tests, the animals were decapitated for neurochemical studies, wherein EGR-1 protein expression in the hippocampus and prefrontal cortex was evaluated. The results showed that SST administration significantly improved deficits in sociability, attention-deficit-like behavior, and fear memory. Furthermore, reduced EGR-1 expression levels due to isolation stress were observed, which were restored by SST administration, suggesting that SST may be beneficial for the treatment of some ADHD symptoms (Fujiwara et al. 2018).

Ziziphus jujuba Mill. var. *spinosa*—inflammatory processes

Kandeda et al. (2021) investigated the anti-amnesic and molecular effects of aqueous extract of *Ziziphus jujuba* on D-galactose-induced working memory impairment in rats. The animals were treated with aqueous extract (41.5, 83, and 166 mg/kg, orally) daily for 14 days. At the end of the treatments, pro-inflammatory and neuronal damage markers were analyzed in the prefrontal cortex. The results showed that D-galactose caused working memory deficit along with alterations in tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interferon-gamma (IFN-γ). Treatment with the extract (166 mg/kg) reversed the working memory deficit and normalized levels of TNF-α, IL-6, and IFN-γ, thereby mitigating neuroinflammation. Tran et al. (2019) conducted a study to evaluate three new sesquilignan compounds from Z. jujuba for their bioactivity, including anti-inflammatory effects and cytotoxic activities. Here, we will report the anti-inflammatory findings. The authors used RAW264.7 cells and induced inflammation with LPS. First, they determined the IC50 of 18 compounds for NO inhibition and found NO inhibition in two compounds at concentrations ranging from 18.1 to 66.4 µM/mL. They then evaluated iNOS and COX-2 expressions and observed a decrease in the expression of iNOS and COX-2.

Conclusion

In summary, the all the studies included in this review focused on plants with demonstrated potential against inflammatory processes, positioning them as promising candidates for ADHD treatment, especially in patients who may not respond well to conventional medications.

The utilization of plants for medicinal purposes has a long history in human culture. In the context of ADHD treatment,

natural products may play a role in attenuating or preventing the neuroinflammatory mechanisms. They have shown the capacity to positively modulate various inflammatory mediators, including cytokines, chemokines, and cytotoxic molecules, such as cyclooxygenase-2 (COX-2), reactive oxygen species (ROS), glutamate, and prostaglandins. Additionally, plant based medicines can impact specific signaling pathways like Toll-like receptor 4 (TLR4) and Mitogen-Activated Protein Kinases (MAPK), among others outlined in this review.

It's important to note, however, that while natural medicines are generally considered safe, they have not yet reached the status of a standard therapeutic resource for ADHD. This may be attributed to several factors, including the limited number of human clinical studies available, often with small sample sizes. Additionally, some of these studies lack proper control groups and exhibit inconsistent results. Furthermore, there is a dearth of initial studies elucidating the mechanisms of action of plant-derived compounds on the CNS, and there is no established standard animal or in vitro experimental model for studying ADHD.

Further studies are needed with the plants presented here. Future investigations should employ more rigorous and controlled methodologies to comprehensively evaluate the effectiveness of these alternative treatments and elucidate their mechanisms of action. This will facilitate equitable comparisons with existing studies and conventional ADHD medications, ultimately enhancing our knowledge of their therapeutic potential.

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Data availability Data sharing not applicable.

Declarations

Conflict of interest No potential conflict of interest was reported by the author(s).

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