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ADHD (P ROBAEY, SECTION EDITOR)

Complementary and Alternative Medicine use in Pediatric Attention-Deficit Hyperactivity Disorder (ADHD): Reviewing the Safety and Efficacy of Herbal Medicines

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Abstract Natural health products (NHPs), including herbal medicines, are a modality of complementary and alternative medicine (CAM) commonly used by pediatric patients with attention-deficit hyperactivity disorder (ADHD). Most families of pediatric patients find NHP treatment to be beneficial; however, clinical evidence of efficacy remains weak or lacking. Evidence of herbal medicine safety is similarly scarce, particularly with respect to herb-drug interactions and adverse events (AEs) associated with concurrent use of NHPs and ADHD prescription drugs. To support both families and physicians managing ADHD care, this review focuses on integrating available data on the safety and efficacy of herbal medicines commonly used by pediatric ADHD patients. In addition to reviewing results from clinical trials, patient surveys, and experimental studies relating to commonly used herbal medicines, the paper discusses adverse event reports involving concurrent use of herbs and ADHD drugs, identified through the FDAble database. While NHP and other CAM offer patients alternative treatment options with potential benefits as well as risks, additional research is needed to support open discussion and evidence-based decision making by families and physicians.

Keywords Attention-deficit hyperactivity disorder (ADHD) · Complementary and alternative medicine (CAM) · Natural health products (NHPs) · Herbal medicines · Adverse events (AEs) · Herb-drug interactions · Efficacy · Pediatric

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Introduction

According to the National Centre for Complementary and Alternative Medicine, complementary and alternative medicine (CAM) represents a group of diverse health and medical systems, practices, and products that are not part of conventional (allopathic) medicine but used alongside or in place of conventional medicine [1]. Accordingly, CAM serves as an umbrella term encompassing various categories: biologically based practices or natural health products (NHPs) (e.g., herbal medicines, vitamins), mind-body medicine (e.g., yoga, relaxation), manipulative and body-based practices (e.g., chiropractic, osteopathy), energy medicine (e.g., Qigong, magnets), and whole medical systems (e.g., homeopathy, naturopathy) [1, 2].

The use of CAM is not only widespread among adults but also children (including youth). Based on recent studies, up to 40 % of healthy children and up to 75 % of children with chronic disorders utilize one CAM modality or another, with some using 2 or more simultaneously [3–14, 15•]. CAM use is especially high in pediatric patients with developmental disorders, a trend due, in part, to the chronic nature of disease and treatment, the occurrence of comorbid conditions, the desire of parents to try anything that may help their child, and

concerns about adverse events related to prescribed pharmacotherapy [16–18]. Among this population, attention-deficit hyperactivity disorder (ADHD) patients are among the most common users of CAM practices [19•].

CAM Use in Pediatric Psychiatry and ADHD

Surveys aiming specifically to identify determinants of CAM use among pediatric ADHD patients, though few in number, reveal that 54–68 % of families report giving their child at least one type of CAM over the previous year [16, 18] or over their lifetime [17]. Children with an ADHD diagnosis are also more likely to receive CAM treatment than children in whom ADHD is suspected or who display problematic behaviors, as indicated by parents [20]. The most commonly reported CAM modalities were vitamins and dietary supplements, herbal medicines, sensory integration, occupational therapy, art, music, special exercises, relaxation, prayer, biofeedback, chiropractic, massage, and hypnosis [16–18]. When asked why they opted for CAM, families most frequently referred to preference for more natural therapy, desire for control over treatment, minimization of symptoms, cultural/family tradition, recommendation by friends or family, concerns regarding side effects of conventional drugs, hope for cure, and recommendation by physicians or CAM practitioners [16–18]. Since these studies focused on ADHD symptom management, however, they may not capture CAM use for treatment of comorbid conditions, disease prevention, or health maintenance and consequently underestimate overall use.

Looking more broadly at the pediatric psychiatry population, the use of CAM again appears prevalent, as does its combination with pharmacoptherapy. A recent study in Canada identified that 48–78 % patients had used CAM—with most finding it helpful—and that 46 % had done so concurrently with conventional medicine [21•]. Whereas many patients and families report CAM-related benefits, adverse events (AEs) are also well documented. Among 80 AEs reported by pediatric specialty outpatients—40 % of which were self-reported as moderate or severe—56 % involved concomitant use of CAM with prescription drugs [22•]. An Australian study of CAM-related pediatric AEs reported 39 relevant cases; 64 % were severe, life threatening, or fatal; and 77 % were considered probably or definitely related to CAM use [23]. The four fatalities were deemed to have resulted from failure to use conventional medicine in favor of CAM.

The use of CAM in pediatric ADHD is clearly widespread, whether for symptom management, health maintenance, or prevention of concomitant conditions such as sleep problems, depression, anxiety, or conduct disorders [24]. Despite this prevalence, only 30–65 % of families discuss pediatric CAM use with a physician [21•, 22•, 25, 26]. Clinicians, on the other hand, may be similarly disinclined to discuss CAM use due to their personal beliefs or lack of knowledge about the topic; indeed, less than 5 % of pediatricians report feeling "very knowledgeable" about CAM therapies [25, 27]. This frequent lack of communication is of particular concern since ADHD drugs are administered over long periods of time, and at times in cocktails. The addition of CAM to the mix can potentially improve symptoms or general health but can also increase the risk of drug interactions and AEs [22•, 28, 29]. Accordingly, both patients and practitioners must be well informed and maintain an open dialogue about alternative treatments.

Unfortunately, the evidence to support conversations about CAM safety and efficacy in ADHD is generally dispersed, weak, or incomplete. As an initial step toward filling this gap, this review focuses on herbal medicines, synthesizing available data regarding the safety and efficacy of botanicals commonly used by pediatric ADHD patients.

Herbal Medicines in ADHD

Why Focus on Herbal Medicines?

Herbal medicines (HMs) are often perceived as "natural" and "safe," leading to fewer AEs compared to conventional medicine [24]. Similar to prescription drugs but unlike many types of CAM, HM, and other NHPs contain raw or processed medicinal and nonmedicinal substances, many of which are bioactive and can elicit pharmacokinetic and pharmacodynamic responses [30]. Once consumed, such substances are absorbed, distributed, metabolized, and eliminated by the body, often inhibiting or inducing metabolic enzymes or transporters. Many of these substances also possess bioactivity as ligands for receptor targets leading to molecular and physiological effects [29]. Whereas herbal medicines may contribute to symptom control for some patients, they may also lead to toxicity or affect the safety and efficacy of other medicines [31].

Given that HMs are among the most common form of CAM used in combination with both psychostimulants and nonstimulants, the potential for herb-drug interactions is prevalent [21]. Because most HMs are chemically complex and, in some jurisdictions, are not rigorously regulated for quality control, the chemistry, potency, and safety of any given HM can vary from one product to the next. Differences in plant chemistry may arise due to genetics, geography, and environmental factors, as well as harvesting, storage, manufacturing, and formulation practices [32]. This variability can influence patient response and health [30, 33, 34], more frequently if the product is adulterated, used inappropriately, long-term, or concurrently with prescription drugs (especially those with narrow therapeutic indices) [29].

Commonly Used Herbal Medicines by ADHD Patients

Among pediatric ADHD and other pediatric psychiatry patients, some of the most commonly used HM include St. John's wort, chamomile, rhodiola, valerian, bacopa, pycnogenol, kava kava, *Ginkgo biloba*, ginseng, evening primrose oil, lemon balm, echinacea, goldenseal, peppermint, rosemary, green tea, garlic, eleuthero, linden, skullcap, ginger, and passion flower [18, 21•, 25, 26, 33, 35]. Whereas many of these HMs are utilized for ADHD-specific symptom management, others (e.g., ginseng, goldenseal) are considered adaptogens useful in health maintenance and disease prevention. Cala et al. [26] reported that treatment of ADHD symptoms accounts for only 35 % of HM consumption by pediatric ADHD patients, citing treatment of colds, rashes, fevers, asthma, insomnia, and allergies, as well as the maintenance of general health as other reasons for HM use. More studies examining this type of CAM use are needed to better understand if these results extend to other populations [26].

Evidence of Herbal Medicine Efficacy in ADHD

Traditional uses of HM usually provide the basis of evidence for their utility in the management of ADHD symptoms. For example, restlessness, poor concentration, and sleep difficulties commonly seen in ADHD patients may improve with the use of a sedative herb such as kava kava, chamomile, or valerian, which possess anxiolytic properties (but have not been validated through ADHD clinical trials) [25]. Evidence from randomized placebo-controlled trials, a current requirement for determining the therapeutic efficacy of drugs, is scarce with only a few popular herbs evaluated to this standard for ADHD. Most clinical trials examining the efficacy of HM in ADHD, whether yielding positive or negative results, suffer from inadequate trial design (e.g., small subject sample size, short duration, inadequate dose) [36•], incomplete reporting, and risk of bias (e.g., poor or no subject blinding) [37]. Other limitations may include the lack of appropriate control group (or undocumented), concurrent use of ADHD pharmacotherapies, and few examples of head-to-head trials with approved drugs [38–41].

The effectiveness of HM (and other CAM) for ADHD symptom management has been reviewed elsewhere (refer to [38–40]). To focus on pediatric research, Table 1 summarizes the results of identified clinical trials using herbs for ADHD in children, highlighting reported results as well as study weaknesses. *Gikgo biloba*, for example, was effective at reducing inattention scores of subjects compared to placebo in one randomized, controlled, double-blind study [46] but less effective at reducing symptoms in a separate parallel-group, randomized, double-blind study [47]. Both studies had a short duration of intervention (6 weeks) and a small subject sample size. In a small ($n = 18$) 4-week, randomized double-blind, double-crossover trial, evening primrose oil showed no significant differences in symptoms relative to D-amphetamine but also placebo [44]. A 15-week randomized, placebo-controlled, double-blind trial of evening primrose oil with 132 subjects reported significant medium to strong effects in reducing ADHD symptoms compared to placebo [45]. Although the sample size in this study was larger, the subjects did not show severe ADHD symptoms at baseline. Overall, evidence for the efficacy of HM in the treatment of pediatric ADHD in well-designed trials is limited and generally weak.

Despite the lack of clinically proven efficacy, HM may offer benefits to some patients and serve as an option for the 10–30 % of ADHD patients who do not respond to stimulant drugs or who experience intolerable AEs [54]. As stated, many patients also use HM to treat comorbid conditions and symptoms that extend beyond core symptomology and thus available clinical trial data. Importantly, ADHD patients who use HM (and CAM) generally perceive them to be beneficial. For example, in three independent pediatric neurology studies, HM were reportedly perceived by families to be helpful for 50–78 % of children who use them [21•, 26, 55]. Given the popularity of HM and their perceived benefits, it is crucial to examine the evidence of safety and risk.

Evidence of Herbal Medicine Safety and Risk

As summarized in Table 1, most clinical trial results of HM used for pediatric ADHD report few mild to moderate AEs, generally comparable to placebo, if AEs are reported at all. Notably, an 8-week randomized, controlled, double-blind study examining Ningdong granule reported fewer and milder AEs compared to methylphenidate (MPH) as well as one severe AE [50]. Similarly, multiple trials report fewer side effects such as decreased appetite, anxiety/nervousness and headache among herb- rather than methylphenidate-treated participants. The high degree of reported HM tolerability when administered alone, in moderation, over the short term suggests but does not confirm safety and the frequent failure to report AEs may reflect either poor safety data or poor attention to monitoring and reporting. Importantly, in addition to potentially toxic effects at high doses, HM pose a risk of AEs due to interactions with prescribed drugs.

Mechanisms of Herb-Drug Interactions Similar to typical drug-drug interactions [28], HM (or components thereof) can interact with drugs at the pharmacodynamic level, with one acting synergistically or antagonistically to the other. For example, combining Ephedra (which contains ephedrine) with another stimulant will enhance effects on heart rate and blood pressure as well as risk of related AEs. More frequently, however, herb-drug interactions (as well as other NHP-drug interactions) occur at the pharmacokinetic level. As substrates, inhibitors, and inducers of drug metabolizing enzymes and transporters, NHPs can increase or decrease drug

Table 1 Summarized results of clinical trials of herbal medicines used for pediatric ADHD

Herbal Medicine [reference]	Methodology/ sample size	Duration of treatment	Results	Limitations	Adverse events
Bacopa [42]	Open-label/31	6 months	Effective for assessed ADHD symptoms excluding social problems and well tolerated by children	SS, LP, uncontrolled	N/A
Chamomile (*Matricaria chamomilla*) [43]	PC/3	4 weeks	Improvements in mean scores for hyperactivity, immaturity, and inattention	SS, SD	N/A
Evening primrose oil [44, 45]	R, DB, DCO/18 R, PC, DB/132	4 weeks 15 weeks	No difference compared to placebo or D-amphetamine Significant medium-strong positive treatment effects of core ADHD symptoms compared to placebo	SS, SD Symptoms not severe at baseline	N/A N/A
Ginkgo biloba [46, 47]	PG, R, DB/50 R, PC, DB/66	6 weeks 6 weeks	Less effective than MPH for ADHD (Parent and Teacher Rating Scale) with less frequent reductions in appetite, headache and insomnia More effective than placebo (inattentive scores) and safe	SD, SS SD, SS No drug-free follow-up	10 AEs: mild-moderate, no significant difference between control and experimental Mild, no significant difference between experimental and placebo
Ginseng [48]	DB, R, PC/72	8 weeks	Safe and decreased hyperactivity and impulsivity scores	SS, SD ADHD NOS only	No significant difference between experimental and placebo
Lemon balm Valerian [49]	PR, MC, NI/169	7 weeks	Reduced symptoms of restlessness, concentration difficulties, and impulsivity (standardized Likert-based survey evaluation by parents)	SD, sample did not meet ADHD criteria	Mild AEs in 2 (1.18 %) of patients
Ningdong granule [50]	R, C, DB/72	8 weeks	Effective reduction in ADHD symptoms (Teacher and Parent ADHD Rating Scale) and safe short term	SS, SD	Mild, fewer AEs compared to MPH, 1 severe AE
Passion flower [51]	PG, R/34	8 weeks	No difference between treatment and MPH, both groups improved from baseline, more decreased appetite and anxiety with MPH	SS, SD, fixed dose	No significant difference between experimental and MPH
Pycnogenol [52]	R, DB, PC/61	4 weeks	Significant reductions in hyperactivity, visual motor coordination, attention, and concentration (not observed with placebo), some symptoms returned following discountinuation	SS, SD	Mild to moderate in 2/61 patients
St. John's wort [53]	DB, R, PC/54	8 weeks	No significant improvement (ADHD Rating Scale-IV & Clinical Global Impression Improvement Scale)	SD SS	No significant difference between experimental and placebo

PG parallel group, *R* randomized, *DB* double blind, *DCO* double cross over, *PC* placebo controlled, *PR* prospective, *MC* multicenter, *NI* noninterventional, *C* controlled, *SD* short duration, *SS* small sample size, *LP* lack of placebo, *nos* not otherwise specified, *N/A* not available, *MPH* methylphenidate

bioavailability and alter efficacy and safety by proxy [56]. Such interactions may not always equate to a clinically significant drug interaction and depends largely on the therapeutic index of the drug and degree of change in systemic exposure [56, 57].

Both acute and chronic use of HM can impact the disposition of prescribed drugs. Acute administration may cause AEs through increased or decreasing drug metabolism and clearance, but chronic administration may lead to a biphasic response where both toxicity and efficacy may decrease [58].

Experimental Evidence of Risk Knowledge about the clearance of ADHD pharmacotherapies is fundamental to examining related risks of herb-drug interactions. Considering the importance of the hepatic cytochrome P450 (CYP) system in drug metabolism, drug-drug, and herb-drug interactions, there is a dearth of available information on the CYP profiles of several approved ADHD drugs, with few comprehensive published data for either MPH or amphetamine currently available in the public domain.

Briefly, MPH is extensively metabolized by carboxylesterase 1A1 [59], an enzyme whose substrate/inhibitor profile is poorly characterized [60], but other enzymes may also be involved. Amphetamine is metabolized extensively by CYP2D6 in mice and rats, but to a minor extent in humans [61–63], where it may also act as a weak inhibitor [64]. Lisdexamfetamine, an amphetamine pro-drug, does not appear to be metabolized by human liver homogenate, hepatocytes, or microsomes [65], nor does it significantly interfere with the

metabolism of specific CYP substrates [66]. The metabolism of atomoxetine is better characterized, with CYP2D6 generating the primary metabolite [67] and a corresponding bimodal distribution of pharmacokinetic parameters reflecting CYP2D6 poor and extensive metabolizers [68, 69]. Another major nonstimulant medication, guanfacine, is metabolized primarily via CYP3A4 according to the product monograph [70].

Several HMs commonly used in ADHD management are known to inhibit or induce phase 1 and/or 2 enzymes involved in drug metabolism (Table 2). There is a lack of evidence supporting direct effects of HM in the pharmacokinetics of ADHD drugs specifically, with most evidence derived from in vitro studies targeting CYP isozyme activity and inhibition. The impact of HM on carboxylesterases responsible for MPH metabolism remains unclear. Many herb-drug interactions observed in vitro, however, are not confirmed in vivo [28]. In vitro approaches using microsomal assays and primary cultures of human hepatocytes provide mechanistic insight on potential herb-drug interactions that can inform human studies and clinical practice [56]. Standing alone, in vitro data (Table 2), suggest a potential risk that requires experimental or clinical corroboration.

Clinical Evidence of Risk Adverse events, specifically drug interactions, are a major cause of patient morbidity and mortality. An estimated 1.5 million adults in the USA are at risk for possible AEs resulting from interactions between prescription drugs and NHPs, and these statistics are unknown for pediatric populations [85]. In a large pediatric emergency room study in Canada, approximately 20 % of pediatric patients used medications with one or more NHPs and, based on 35 reported herb-drug interactions, most were pharmacokinetic in nature (e.g., modified drug absorption) [86]. Two studies of pediatric adverse events related to CAM found that HM were linked to 1 of 19 moderate AEs [21•] and 12 of 39 total AEs [23], respectively. The high frequency of concurrent drug and HM use by pediatric ADHD patients and related risk of herb-drug interactions and AE warrants further investigation and monitoring.

Notably, less than 10 % of all AEs are reported. AEs involving both NHPs and prescription drugs are reported even less frequently, estimated at <1 % of their occurrence [87]. Whereas this scarcity of NHP-related AEs compared to pharmaceuticals may reflect less toxic potential, several factors contribute to the under reporting of such events: healthcare practitioners may be unaware of patients' NHP use or unaware of a patient experiencing an AE unless it is serious enough to demand clinical attention; exacerbation of an AE by a NHP may simply be attributed to the drug; uncertainty about causality; time pressure in the workplace; or lack of patient awareness about NHP use and risks [14, 23, 57, 88, 89].

Searching the FDAble Adverse Events Database Given the widespread use of HM among pediatric ADHD patients yet the dearth of published AE studies in North America, the FDAble adverse events database was examined to gauge the frequency and severity of AEs involving the concurrent use of HM and ADHD pharmacotherapy, including potential herb-drug interactions. We systematically searched the database (http://www.fdable.com) for reports involving one (or more) of 22 different HMs commonly used by ADHD patients, specifically, and children, more generally. Using the advanced search option, we targeted each herbal by name (common and scientific) and recorded the total number of AEs reported for patients of 0–18 years (Fig. 1). From these reports, we identified those that also involved ADHD medications (methylphenidate: Concerta, Metadate, Ritalin, Focalin, Quillivant, Daytrana, and Methyllin; amphetamine: Adderall, Dexedrine, ProCentra, Zenzedi, and Dextrostat; methamphetamine: Desoxyn; lisdexamfetamine: Vyvanse; guanfacine: Intuniv; atomoxetine: Strattera). Note that, due to the limited data available for each report, we are unable to determine any degree of causality relating to potential herb-drug interactions.

Among the 22 targeted HMs, 167 adverse event reports (AERs) were identified for pediatric patients (Fig. 1). No AERs were found for bacopa, eleuthro, linden, rosemary, and skullcap. Goldenseal, lemon balm, pycnogenol, and rhodiola had one AER and none of these involved ADHD drugs. Approximately 12 % of the identified AE reports involved both a HM and an ADHD drug. Echinacea, *Ginkgo biloba*, garlic, St. John's wort, evening primrose oil, and ginseng were involved in AERs with ADHD drugs. MPH was a suspect drug with 11 of the 20 AERs and was involved with each of the herbal medicines mentioned above. Atomoxetine and amphetamine were the suspect drugs in seven and two reports, respectively. The most frequent herb-drug AER combinations were evening primrose oil with MPH, and ginseng with atomoxetine (three cases each). In most cases, additional substances were reported beyond herbal medicine and ADHD drug. The frequency of total and ADHD drug-related AERs for different HM may reflect their relative frequency of use by pediatric patients as much or more than their relative risk of toxicity. Similarly, chamomile—a HM commonly used to calm children—was identified in the most total AERs yet no ADHD-related AER. While this finding suggests that chamomile is relatively safe, it does not indicate

Table 2 In vitro herb-drug interaction studies highlighting common herbal medicines and reported modulatory effects on ADHD drug-metabolizing CYP enzymes

Herbal Medicine [reference]	Enzymes tested (CYP)	Conclusions
Bacopa [71]	**3A4**[a], 2C9, 2C19, 1A2, **2D6**[b]	Moderate inhibition with 3A4, 2C9 and 2C19, 1A2
		Use with caution when administered concurrently
Echinacea [72]	1A2, **2D6**, 2E1, **3A4**	Slight modulatory effect on 2D6 and 2E1
		Minor effect on 1A2 and 3A4
		Concomitant administration with conventional drugs not recommended
Eleuthero [73]	2C9, **2D6**, 2E1, and **3A4**	No effects on 2D6, 3A4
		Weak inhibitory effect on 2C9 and 2E1
Evening primrose oil [74]	1A2, 2C9, 2C19, **2D6**, **3A4**	Potential to inhibit the metabolism of coadministered medications
Garlic [75]	2C9, **3A4**	Suppresses CYP2C9 and CYP3A4 not affected
		Concurrent administration with CYP2C9 substrates may cause adverse drug reactions
Ginkgo biloba [76]	1A2, **3A**, 2C9	Enzymes not significantly inhibited by major components of preparations in clinical use
		Significant inhibitors include flavonol aglycones, biflavonol, amentoflavone, and other nonglycosidic constituents
Ginseng [77]	1A2, **2D6**, 2E1, **3A4**	Clinically significant interactions are unlikely
Goldenseal [77]	1A2, **2D6**, 2E1, **3A4**	Strong inhibition of 3A4 and 2D6 substrates
		Serious adverse events may occur from concurrent use with substrates
Green tea [78]	2B6, 2C8, 2C19, **2D6**, **3A**	Catechins have potential for clinically relevant interactions for 2B6, 2C8, and 3A4 substrates
Kava kava [79]	1A2, 2C9, **2D6**, **3A4**, 4A9/11, 2A6, 2C8, 2E1	High potential for drug interactions
Peppermint oil [80]	**3A4**	Moderate and reversible inhibitor
Rhodiola [81, 82]	**2D6**	Rhodiosin and rhodionin noncompetitive inhibitors
	3A4	Potential for drug interactions
		Potential for clinically relevant drug interactions
St. John's wort [83,84]	1A2, 2C9, 2C19, **2D6**, **3A4**	High inhibition potential for 3A4, 2C9, and 2D6
	1A2, 2C9, **2D6**, **3A4**	Inhibition and induction potential for 3A4
Valerian [77]	**3A**4/5, 1A2, 2E1, **2D6**	Typical doses of valerian are unlikely to cause clinically significant effects on metabolism of 2D6 and 3A4/5

[a] CYP3A4 is the metabolizing enzyme of guanfacine

[b] CYP2D6 is the metabolizing enzyme of amphetamine and atomoxetine

an absence of risk. Although causality cannot be determined based on the FDAble data, potential herb-drug interactions identified through the database (e.g., evening primrose oil with MPH and ginseng with atomoxetine) warrant further investigation, particularly since all six herbs involved in ADHD drug-related AER (Fig. 1) are

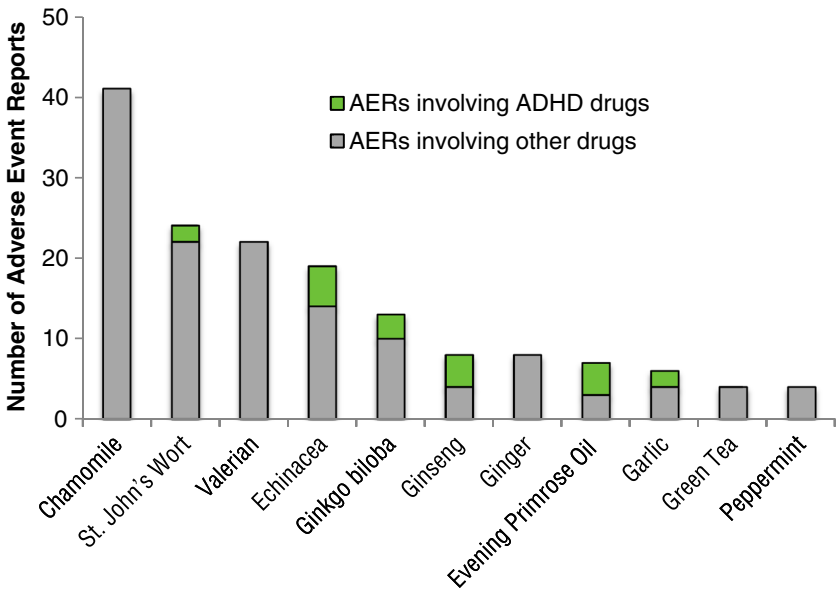

Fig. 1 Total adverse event reports (AERs) and adverse event reports involving ADHD drugs for common herbal medicines within the pediatric population (age 0–18), as identified through the FDAble database (http://www.fdable.com)

known to modulate at least some ADHD drug metabolizing enzymes in vitro (Table 2).

Closing Remarks

Knowledge Gaps in the Field

Numerous knowledge gaps obscure our understanding of the potential benefits and risks of HM use in pediatric ADHD yet highlight needed avenues of future research. The need for more clinical evidence of efficacy and safety in high-quality pediatric ADHD trials is paramount, including comparative trials with standard ADHD pharmacotherapies. Adverse events are broadly under reported and those involving HM and other NHP can be more difficult to report and interpret since information about ingredients or formulations is not always readily available. Regulatory standards and frameworks to facilitate accurate reporting of AEs involving HM and CAM, in general, must be implemented and supported to strengthen existing monitoring and surveillance programs [23]. While tools like the FDAble AER database offers access to standardized case data, individual reports lack sufficient detail to evaluate any degree of causality or interaction.

The direct effects of herbal medicines on ADHD drugs in clinical and experimental models are also urgently needed. Whereas indirect in vitro approaches using marker probe substrates provide insight on potential risk, the effect of HM on ADHD drug metabolism remains mostly unstudied. In vitro models, although informative, do not always reflect specific effects on different drugs or, more importantly, the potential clinical significance of observed interactions. A more complete understanding of ADHD drug metabolism is therefore also needed.

Doctor-Patient Communication

As with any treatment, the use of HM by children with ADHD should be monitored by families and practitioners to evaluate safety and efficacy, especially when stimulant or nonstimulant medications are or will be used as well. Open communication between patients, families, and physicians is an essential component of mitigating risk and benefit. However, while healthcare providers are their preferred and most trusted source of medical advice, the majority of families do not discuss the concurrent use of CAM and prescription medicines with a medical doctor [21•].

Research indicates that most families expect physicians to ask them about CAM use in a nonjudgmental fashion. Families also do not expect physicians to be experts in the field of CAM, but rather be open to discussion and provide advice on efficacy and safety [90]. In order to better advise families, physicians should be aware of available tools to facilitate communication and access information about commonly used NHPs and the possible interactions with prescription drugs [21•,90,91]. As is often available for prescription drugs, healthcare providers could offer educational resources regarding CAM to patients and families in the clinic (brochures, direction to credible websites, publications, etc.). In doing so, patients can be well informed and may feel more comfortable initiating a discussion about CAM with their physician.

Conclusion

Patients and families using or interested in using HM and other NHP or CAM should not be dismissed or discouraged blindly from doing so; potential benefits and risks should be discussed and weighed—keeping in mind potential interactions with substances taken concomitantly. If not yet offered by patients or families, healthcare providers should, whenever possible, initiate a conversation about CAM. With the high prevalence of HM use in pediatric ADHD, limited clinical evidence yet family-reported benefits, and risks of herb-drug interactions, more research is needed in order to support evidence-based decision making and effective communication between patients, families, and doctors.

Compliance with Ethics Guidelines

Conflict of Interest Hajra Mazhar, Emerson F. Harkin, Brian C. Foster, and Cory S. Harris declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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