Herbs for Attention-Deficit/ Hyperactivity Disorder

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Abstract

Nootropic herbs can be very helpful in people with attention-deficient/hyperactivity disorder (ADHD). Two herbs both called brahmi in the Ayurvedic tradition, *Bacopa monnieri* (bacopa) and *Centella asiatica* (gotu kola), as well as formulas featuring these herbs, are discussed in great depth for this purpose. Additional general nootropic herbs discussed are *Ginkgo biloba* (ginkgo) and *Acorus calamus* (sweetflag), including both American and Eurasian varieties. Nootropic herbs from the Lamiaceae (mint) family with a focus on *Rosmarinus officinalis* (rosemary) and various species of *Salvia* (sage) are also reviewed. The general failure of nervine herbs such as *Hypericum perforatum* (St. John's wort) and *Valeriana officinalis* (valerian) for ADHD is highlighted, giving further impetus for the need to focus on nootropic herbs instead. The safety and clinical use of all relevant herbs is highlighted.

Keywords: attention-deficit/hyperactivity disorder, herbal medicine, nootropic

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a fairly self-explanatory though controversial condition. According to the *Diagnostic and Statistical Manual IV*, it requires the presence of six or more of a list of symptoms of inattention and/or hyperactivity/impulsivity for at least six months (with onset prior to seven years of age), with these symptoms being more severe than that of peers at a similar developmental age. The symptoms result in impaired function in two or more settings (home, school, and/or work). The *Diagnostic and Statistical Manual V* broadened the diagnosis, saying symptoms only had to be present prior to 12 years of age, thus opening the diagnosis to adolescents and adults, and requiring only five or more symptoms of inattention or hyperactivity/impulsivity to be present for diagnosis. It now requires impairment in only one setting, and adds mild, moderate, and severe categories based on degree of dysfunction, as well as specifying three subtypes: predominantly inattentive, predominantly hyperactive-impulsive, and combined.

As with most mental health conditions, there is no gold standard test available against which to compare these criteria to determine if they are accurate. Though studies have been done to validate the criteria, the ongoing problem of what to validate them in relation to remains a sticking point.[1] In the real world, diagnoses are often made relatively quickly, particularly without ruling out complicating diagnoses such as learning disabilities, posttraumatic stress, and anxiety. The extremely variable rates of diagnosis of ADHD between U.S. states, ranging from a low of 4.2% in Nevada to a high of 14.8% in Kentucky, raise questions about the accuracy of diagnoses.[2] Studies around the world documenting that younger children within a grade cohort are far more likely to be diagnosed than older children suggests a fair number of relatively immature children are being inappropriately diagnosed with ADHD.[3–5] Even more troubling is ample evidence that pharmaceutical companies selling medications for ADHD have used various nefarious means to drive over-diagnosis and over-treatment.[6,7]

This article will focus on treating those children and adults who truly have ADHD. Large, carefully conducted surveys in predominantly white and predominantly African American children in North Carolina suggest a prevalence of ADHD of 1–3% (with significantly more boys than girls being affected).[8,9] This group may benefit from stimulant medications, which work, it is believed, primarily by affecting dopamine metabolism in the central nervous system and not because they are stimulants. However, following the naturopathic principle of using the least force necessary, starting with safer options including herbal medicines is reasonable. Medications can always be prescribed later if herbs or other low-force options do not work. Dietary changes and nutrient therapies, such as hypoallergenic diets and omega 3 fatty acids, also play an important role in helping many people with ADHD, but are beyond the scope of this article.[10,11]

Nootropic Herbs: The Brahmis

The primary herbal treatments for ADHD are nootropics. These are herbs that enhance cognitive function and memory, though they appear generally to have other beneficial effects, including supporting nerve regeneration and growth. Many clinicians reach first for nervine herbs (those that calm the nervous system), but generally these are not nearly as effective,

if at all, for people with ADHD. Nervines are discussed in more detail below. The exact biomolecular mechanisms of action of nootropics are fairly poorly researched but will be discussed where known.

Bacopa monnieri (bacopa, brahmi) in the Plantaginaceae family is perhaps the best-studied nootropic for ADHD patients. It is native to tropical wetlands around the world, though it is most notable for its historical use in India. Its Latin name is frequently misspelled *B. monniera*. The whole plant (leaf, flower, stem, and root) are used as medicine.

Bacopa has a strong historical reputation for enhancing memory.[12] A meta-analysis of nine high-quality trials involving 437 subjects found clear evidence that bacopa extracts significantly improved cognitive function compared to placebo, though the effect size was modest.[13] Seven of the studies involved healthy subjects and two patients with memory problems. The studies took place in Australia, India, Thailand, and the United States, so the results appear fairly generalizable across diverse populations. Most of the extracts studied were concentrated crude extracts, while three used extracts standardized to $\geq 50\%$ bacoside content. Doses ranged from 250 to 600 mg daily. Only minor adverse effects were reported in these trials, primarily digestive upset.

Another meta-analysis looked at five clinical trials involving 175 children and adolescents, many with diagnosed ADHD.[14] Three of the trials were double-blind and randomized, while two were open trials. There was significant improvement in cognitive and memory function compared to placebo, as well as decreased hyperactivity and attention deficit. The effect sizes of improvement ranged from modest to moderate depending on the specific measures used. A range of extracts and doses were used. Again, adverse effects were mild and uncommon, with only 2.3% of total participants reporting that any occurred. As will be discussed below, various herbal formulas featuring bacopa have also demonstrated efficacy at improving ADHD.

Mechanistically, the triterpenoid saponins known as bacosides from bacopa have demonstrated neuroprotective effects.[15] Evidence exists for other mechanisms of action including increasing cerebral blood flow, restoring cholinergic function, modulating GABA and/or serotonin levels, reducing β-amyloid levels and blocking nerve damage caused by it, reducing free radical damage, altering brain stress hormone levels, and decreasing neuroinflammation.[16,17]

Centella asiatica (gotu kola) shares numerous similarities with bacopa, though it is in the Apiaceae family. Gotu kola is also a tropical species that likely originated in Southeast Asia, but has now become quite a bit more widespread. It prefers to grow in extremely wet places. The entire plant is also used as medicine: leaves, flowers, stems, and roots. Gotu kola is also sometimes called brahmi, further highlighting its similarity in actions to *B. monnieri*. Like bacopa, it contains triterpenoid saponins, though they are ursane not dammarane type. The principal saponins in gotu kola are known as asiaticoside, asiatic acid, madecassoside, and madecassic acid.

Research on the nootropic effects of gotu kola by itself is not as extensive as on bacopa. One clinical trial randomized 28 healthy, elderly adults to gotu kola extract at three different doses or placebo, and found the highest dose (750 mg once daily) significantly improved memory and cognitive function compared to placebo.[18] An older trial found gotu kola improved cognitive function in mentally handicapped children.[19]

One trial looked at a combination of *Ginkgo biloba* (ginkgo) leaf extract (240 mg daily) together with very low doses of gotu kola (68 mg daily) and docosahexaenoic acid (180 mg daily) from fish oil and found it did not improve cognitive function in older adults without cognitive impairment compared to placebo.[20] Several animal studies suggest gotu kola and its triterpenoids have memory- and cognitive-enhancing properties, in line with its traditional use.[21–23] Gotu kola is extremely safe.

Combination formulas combining bacopa and gotu kola, among many others, have also been studied for children and adolescents with ADHD. One meta-analysis looked at nine trials covering four formulas, all of which contained both bacopa and gotu kola as major ingredients.[24] Five of the trials involved children with ADHD, and four of them found the formulas studied significantly improved behavior (measured by a few different testing scales) compared to placebo. These formulas again had minimal adverse effects. The complete ingredients in the formulas tested are extremely extensive and so are not listed here, but daily bacopa doses ranged from 144 to 864 mg and gotu kola doses ranged from 75 to 200 mg.

Ginkgo

Ginkgo biloba (ginkgo), the sole remaining member of the once globally prolific Ginkgoaceae family, is a well-known tree medicine. A special extract of the leaves standardized to contain 24% flavone glycosides, 6% terpene lactones, and <5 ppm ginkgolic acids (which have urushiol-like toxic effects) has been studied intensively for many purposes, including as a nootropic in patients with dementia and ADHD.

An early open trial found that 240 mg of the extract daily led to modest improvements in 20 children with ADHD.[25] A randomized, double-blind trial of this same extract at a dose of just 80–120 mg daily was compared to placebo in 60 children with ADHD.[26] Ginkgo extract significantly improved the parental and teacher ratings of attention compared to placebo. Adverse effects were minor and not different between the groups. Another double-blind trial compared ginkgo extract at 80–120 mg daily to methylphenidate 20–30 mg daily.[27] Both treatments improved attention compared to baseline, but methylphenidate was significantly superior to ginkgo. The adverse effects of decreased appetite, headache, and insomnia were significantly worse and more common in the methylphenidate group compared to ginkgo. Thus, ginkgo can be a safe treatment in patients with ADHD.

Sweetflag as a Nootropic

Acorus calamus (sweetflag; Fig. 1) is a grass-like wetland plant, the only member in the Acoraceae family. It is either

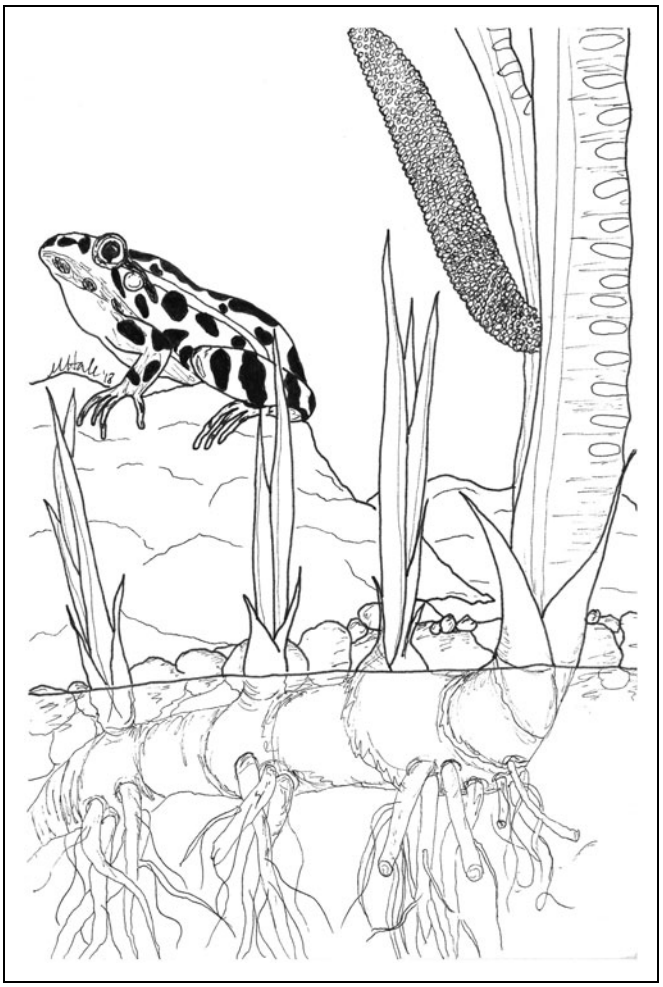

Figure 1. ***Acorus calamus*. Drawing by Meredith Hale and reprinted with permission.**

native all around the Northern Hemisphere or else was introduced from Eurasia into North America. Two varieties are currently recognized and are quite distinct (see Table 1). The difference in chromosome number (ploidy) between the varieties is particularly notable, with a resulting wide difference in the content of β-asarone in the plant's oil. This is important because of concern that β-asarone is carcinogenic.[28,29] However, an isolated constituent is not the same thing as the whole plant, and attributing the effects of the one to the other is fraught with error. Several studies suggest whole sweetflag and its complete volatile oil are actually anti-carcinogenic.[30] Rapid catabolism of β-asarone to non-carcinogenic metabolites may explain the lack of any reports of cancer associated with sweetflag use as food or medicine in humans.[31,32]

Sweetflag is traditionally regarded as a nootropic, neuroprotective, and anti-dementia agent in various cultures around the world.[33] While sweetflag by itself has not been studied in ADHD, a herbal formula known as Shenwu Capsule with substantial amounts of Asian sweetflag has been studied as a nootropic in patients with mild cognitive impairment related to age in two double-blind, randomized, controlled trials.[34,35] Each 450 mg capsule contains *Pueraria montana* var *lobata* (kudzu, gé gēn) root 30%, *Polygonum multiflorum* (polygonum, hiflorum 30%, lsients *A. calamus* var *angustatus* (sweetflag—Asian variety) rhizome 19%, *Epimedium brevicornum* (horny goat weed, yín yáng huò) herb 14%, *Ligusticum chuanxiong* (Szechuan lovage, chuān xiōng) root 14%, and *Panax ginseng* (Asian ginseng, rén shēn) root 4%. The dose used was five capsules q.d. or t.i.d. In one trial, Shenwu was shown just as effective as aniracetam, a nootropic drug, at enhancing memory in 166 subjects. Similarly, the formula was just as effective as donepezil at improving memory and cognitive function in 324 subjects. Studies are needed to confirm these benefits would transfer to ADHD, but clinical experience suggests they would.

A typical dose of tincture of American (diploid) sweetflag is 1 mL t.i.d. It also makes a good cold infusion, and the crude root can be chewed. Despite its name, this herb is not sweet tasting, but somewhat unpleasant and a little bitter. Combination with ginger or another pungent herb is recommended to make it palatable.

Minty Nootropics

Quite a few species in the Lamiaceae family are also nootropic, though they have not been studied formally in ADHD.[36] Clinically they have been helpful, combined with either bacopa or gotu kola and sweetflag. Here, some of the best-known and studied among these herbs will be reviewed. Most of their nootropic effects have focused on their effects in healthy adults or in patients with dementia. These studies do not directly prove a benefit for people with ADHD, but they suggest they are worth studying and trying clinically, supported by empirical evidence that they are helpful for hyperactivity and inattentiveness.

Table 1. β-Asarone Content of Varieties of *Acorus calamus*[a–c]

Variety	Ploidy	Habitat	β-asarone content in oil
Americanus	2n	North America	none
*Angustatus**	3n, rarely 4n, 6n	Europe, India	10–90%

*Also sometimes referred to as *A. tatarinowii*.

[a]Stahl E, Keller K. The classification of calamus. Planta Med 1981;43:128–140 [in German]; [b]McGuffin M, Hobbs C, Upton R, Goldberg A, eds. American Herbal Products Association's Botanical Safety Handbook. Boca Raton, FL: CRC Press, 1997:134–136; [c]Mittal N, Varshney VK, Song BH, Ginwal HS. High levels of diversity in the phytochemistry, ploidy and genetics of the medicinal plant *Acorus calamus* L. Med Aromatic Plants 2015;S1:002.

Rosmarinus officinalis (rosemary) is one such Lamiaceae nootropic. Its association with improved memory was immortalized by one of Ophelia's speeches in Shakespeare's *Hamlet*, when she declares, "There's rosemary, that's for remembrance," and hands some of that plant to her brother Laertes, presumably so he'll remember her in health and not in her depressed, anguished state. Its common name is a folk etymology; it originates from the Latin words *ros* "dew" and *marinus* "sea," referring to its preferred habitat growing at the edge of the Mediterranean. The word sounded a lot like rose, which it is not related to, but the name has stuck. Its leaf, flower, and volatile oil are used as medicine.

Clinical trials with rosemary have focused on memory and cognitive improvement. In one crossover, double-blind, randomized trial, 28 elderly adults were randomized to single doses of powdered rosemary in four amounts or placebo.[37] The lowest dose (750 mg) significantly improved memory compared to placebo, while the highest (6 g) degraded it. Another double-blind trial compared rosemary leaf 500 mg b.i.d. to placebo in 68 university students over one month.[38] Memory, anxiety, and depression all significantly improved in the rosemary group compared to placebo; sleep quality and speed of sleep onset did not differ between them. Compared to no odor, vaporized rosemary volatile oil improved cognitive performance and memory in healthy young adults in another randomized trial.[39] One other trial in 40 healthy young adults with low energy found that single doses of encapsulated rosemary 1.7 g taken while wearing a nose clip to prevent odor identification had no benefit over placebo on mood or congitive effect.[40] There were no significant adverse effects of rosemary in any of these trials. A typical dose of rosemary tincture is 1–2 mL t.i.d., while of crude leaf it is 500 mg b.i.d.–t.i.d.

Animal trials confirm that a rosemary leaf extract inhibits acetyl- and butyrylcholinesterases and leads to enhanced memory.[41] Rosmarinic acid (see Figure 2), a caffeic acid derivative, originally identified in rosemary in 1958 is now known to be prolific in many plants in the Lamiaceae family and contributes to nootropic effects of these herbs.[42] Inhibition of cholinesterases, antioxidant effects, inflammation-modulating effects, and other properties are believed to explain the nootropic effects of rosmarinic acid and related compounds.[43–45] The flavonoid nepitrin from rosemary has also been demonstrated to be nootropic in rodents, in part by inhibiting cholinesterases.[46]

The *Salvia* genus contains multiple nootropic members, particularly *S. officinalis* (common sage) and *S. lavandulaefolia* (Spanish sage) from the Mediterranean basin, *S. apiana* (white sage) from the Sonoran desert, and *S. sclarea* (clary sage) from the Mediterranean and Central Asia among many others.[47] Single doses of Spanish sage volatile oil orally (25–150 mcl) were shown to improve cognitive performance and memory in healthy young adults compared to placebo in two different double-blind trials reported in one paper.[48] A third double-blind, placebo-controlled trial by the same group in 24 healthy adults found similar results with Spanish sage volatile oil.[49] Another double-blind trial involving 36 healthy young adults randomized them to single doses of Spanish sage volatile oil 50 mcl or placebo.[50] They again found significant cognitive benefits of Spanish sage compared to placebo. They demonstrated this specific oil potently inhibited acetylcholinesterase. A comparison of common sage volatile oil inhalation, Spanish sage volatile oil inhalation, and placebo in 135 healthy young adults found that only common sage aromatherapy improved memory compared to placebo.[51] At least two trials have also found common sage helpful for patients with Alzheimer's disease.[52] Doses are very similar to that of rosemary.

Several others in the *Salvia* genus show promise and are listed in Table 2. Combinations of these and other Lamiaceae nootropics show some promise as well. For example, a combination of common sage, rosemary, and lemonbalm improved one measure of memory in the subset of 44 healthy adults <63 years of age in a double-blind, placebo-controlled trial.[53] Massage with lavender and *Pelargonium graveolens* (rose geranium) oil lowered markers of stress and raised serum brain-derived neurotrophic factor significantly compared to no treatment in a group of 25 women with ADHD.[54] Clearly, more research is merited.

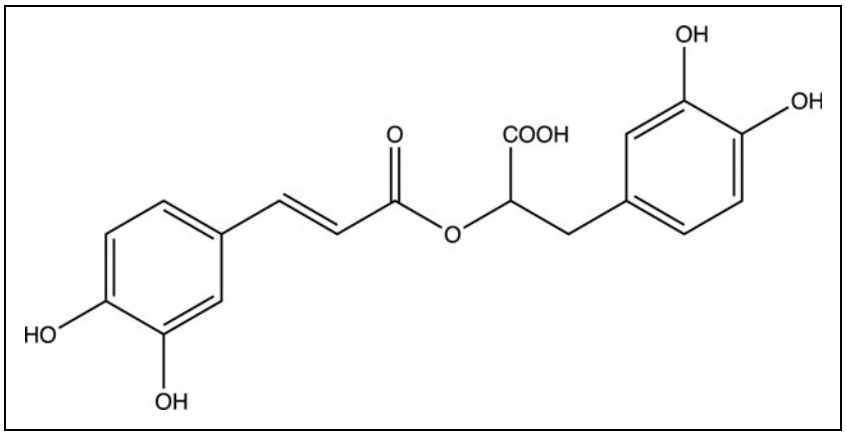

Figure 2. Rosmarinic acid.

Table 2. Miscellaneous Mint Family Nootropics

Herb	Part used	Native habitat	Evidence of nootropic activity
Prunella vulgaris (heal-all)	Leaf/flower	Northern Hemisphere	Qu 2017 (in rats)[a]; Park 2015 (in rats)[b]; Lee 2017 (in vitro)[c]
Melissa officinalis (lemonbalm)	Leaf/flower	Mediterranean basin	Katz 2010 (in humans, combined with other herbs)[d]; Ozarowski 2016 (in rats)[e]
Mentha spicata (spearmint)	Leaf	Eurasia	Herrlinger 2018 (in humans)[f]; Adsersen 2006 (in vitro)[g]
Nepeta menthoides (ostokhodus, Iranian catnip)	Leaf	Iran	Sarahroodi 2012 (in mice)[h]; Ahmadian-Attar 2014 (in rats)[i]
Lavandula angustifolia (lavender) and related species	Leaf/flower	Mediterranean basin	Adsersen 2006 (in vitro)[g]; Dohi 2009 (in vitro)[j]; Xu 2016 (in mice)[k]

[a]Qu Z, Zhang J, Yang H, et al. *Prunella vulgaris* L, an edible and medicinal plant, attenuates scopolamine-induced memory impairment in rats. J Agric Food Chem 2017;65:291–300; [b]Park SJ, Ahn YJ, Lee HE, et al. Standardized *Prunella vulgaris* var *lilacina* extract enhances cognitive performance in normal naive mice. Phytother Res 2015;29:1814–1821; [c]Lee S, Lee D, Baek J, et al. In vitro assessment of selected Korean plants for antioxidant and antiacetylcholinesterase activities. Pharm Biol 2017;55:2205–2210; [d]Katz M, Levine AA, Kol-Degani H, Kav-Venaki L. A compound herbal preparation (CHP) in the treatment of children with ADHD: A randomized controlled trial. J Atten Disord 2010;14:281–291; [e]Ozarowski M, Mikolajczak PL, Piasecka A, et al. Influence of the *Melissa officinalis* leaf extract on long-term memory in scopolamine animal model with assessment of mechanism of action. Evid Based Complement Alternat Med 2016;2016:9729818; [f]Herrlinger KA, Nieman KM, Sanoshy KD, et al. Spearmint extract improves working memory in men and women with age-associated memory impairment. J Altern Complement Med 2018;24:37–47; [g]Adsersen A, Gauguin B, Gudiksen L, Jäger AK. Screening of plants used in Danish folk medicine to treat memory dysfunction for acetylcholinesterase inhibitory activity. J Ethnopharmacol 2006;104:418–422; [h]Sarahroodi S, Jafari-Najafi R, Nasri S, et al. Effects of *Nepeta menthoides* aqueous extract on retention and retrieval of memory in mice. Pak J Biol Sci 2012;15:1085–1089; [i]Ahmadian-Attar MM, Ahmadiani A, Kamalinejad M, et al. Chronic cold-water-induced hypothermia impairs memory retrieval and *Nepeta menthoides* as a traditional "hot" herb reverses the impairment. Iran J Pharm Res 2014;13:185–193; [j]Dohi S, Terasaki M, Makino M. Acetylcholinesterase inhibitory activity and chemical composition of commercial essential oils. J Agric Food Chem 2009;57:4313–4318; [k]Xu P, Wang K, Lu C, et al. Protective effect of lavender oil on scopolamine induced cognitive deficits in mice and H_2O_2 induced cytotoxicity in PC12 cells. J Ethnopharmacol 2016;193:408–415.

Nervines: Far Less Effective

Another group of herbs are traditionally referred to as nervines. We have previously written about these herbs in more depth.[55,56] These herbs are more used for their anxiolytic and sleep-enhancing effects. Though on the surface such herbs would seem well suited to treat ADHD because they are calming, they generally have not proven very effective for ADHD. This is likely due to differences in their effects compared to nootropic herbs.

Hypericum perforatum (St. John's wort) leaf and flower is one such nervine. A small case series suggested that St. John's wort might help teen boys with ADHD.[57] However, a randomized, double-blind trial failed to find any benefit from St. John's wort extract compared to placebo in 54 children with ADHD.[58] *Passiflora incarnata* (passionflower) leaf is another nervine that faired better in the one trial assessing its effects in ADHD. In this one double-blind trial, tablets providing 0.4 mg/kg/day (in two divided doses) of passionflower were compared to methylphenidate 1 mg/kg/day (in two divided doses) in 34 children with ADHD.[59] Both treatments led to equal effectiveness at improving symptoms, while methylphenidate caused significantly more appetite suppression and anxiety compared to passionflower. Another clinical trial failed to find any difference between a dilute tincture of *Valeriana officinalis* (valerian) root and a homeopathic dilution of the same medicine in 30 children with ADHD.[60]

Other nervines have simply not been studied, but it is unlikely they will be as effective as nootropics and so should only be supporting agents in an individualized formula, and not the lead herbs. In some cases, nervines may be useful to treat secondary problems such as insomnia secondary to stimulant medications, though this has not been definitively proven.

Case Study

A four-year-old Jewish boy born with meningomyelocele presented with neurogenic bladder and bowel. No mention was made in the initial visit of the fact he had also been diagnosed with ADHD. He was ambulatory with the assistance of braces and a walker and had a ventriculoperitoneal shunt in place and working well. He was on a combination product containing probiotics, D-mannose, cranberry extract, vitamin C, and some fruit extracts for bladder infection prevention as well as oxybutynin for his neurogenic bladder. The latter drug was causing him to have a dry mouth and to have facial flushing. His father administered him a morning enema to help regulate bowel function, which was time consuming for the family. He was initially started on a combination of gotu kola glycerite 50%, *Astragalus membranaceus* (astragalus) root glycerite 40%, and *Rosmarinus officinalis* (rosemary) leaf tincture 10% at a dose of 2 mL t.i.d. with the goal of trying to restore as much nerve function as possible, as well as a separate tincture of *Atropa belladonna* (belladonna) leaf 5 gtt t.i.d. This replaced the oxybutynin and was slowly titrated up until he hit a dose that managed urination well with just the slightest hint of dry mouth developing.

Over five months of treatment, he gained far superior bladder control with no adverse effects and ultimately got to seven drops t.i.d. of the belladonna tincture safely. His parents noticed good improvement in bowel function and then revealed significant improvement in his ADHD symptoms (including

both reduced hyperkinesis and better focus). This came as quite a surprise, as it had not been brought up as an issue before. His parents were so impressed with the effects, they asked if they could have one of his siblings take the formula for his ADHD.

After six months of treatment, his formula was adjusted to contain *Centella asiatica* (gotu kola) glycerite 30%, *Astragalus membranaceus* (astragalus) glycerite 15%, *Rosa* spp. (rose) glycerite 13%, *Rosmarinus officinalis* (rosemary) tincture 10%, *Nepeta cataria* (catnip) glycerite 12%, *Acorus calamus* var *americanus* (sweetflag) tincture 10%, and *Bacopa monnieri* (bacopa) tincture 10% at a dose of 0.5 tsp t.i.d. The goal was to see if any better results could be obtained with added synergistic herbs. This formula did lead to even better bowel and bladder control, as well as improvement in ADHD symptoms, and has been maintained for more than three years to date, with ongoing excellent results and no adverse effects.

Conclusion

A group of herbs that improve cognitive function known collectively as nootropics are the key to botanical treatment of people with ADHD. Several of these herbs, most notably bacopa and ginkgo, have received moderately good research attention and their benefits for ADHD have been fairly well documented. Even if they are not as potent as amphetamines, they are clearly safer and have a definite role in a holistic treatment protocol for ADHD. Other herbs of the nootropic type that have mostly been studied for dementia and memory loss are clinically helpful for ADHD, but have not been rigorously evaluated for ADHD, including most of the nootropic herbs in the Lamiaceae family reviewed. Ideally one of the better-studied nootropics would be combined with one of the Lamiaceae family nootropics and other less well-confirmed nootropics to create an individualized formula for each ADHD patient.

There is no reason to believe any of the herbs discussed here will interfere with stimulant medications for ADHD. Even St. John's wort, though it is unlikely to help ADHD, is very unlikely to be a problem, as no currently used stimulant is a significant substrate for CYP3A4 (which St. John's wort induces). All the other herbs mentioned here have been used at least empirically with these medications without obvious problems, and there are no published cases or studies showing a problem in that regard. ■

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