

# Effect of the herbal extract combination *Panax quinquefolium* and *Ginkgo biloba* on attention-deficit hyperactivity disorder: a pilot study

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**Objective:** A combination herbal product containing American ginseng extract, *Panax quinquefolium*, (200 mg) and *Ginkgo biloba* extract (50 mg) (AD-FX; CV Technologies, Edmonton, Alta.) was tested for its ability to improve the symptoms of attention-deficit hyperactivity disorder (ADHD). **Design:** Open study. **Patients:** 36 children ranging in age from 3 to 17 years who fit the diagnostic criteria for ADHD. **Interventions:** AD-FX capsules were taken twice a day on an empty stomach for 4 weeks. Patients were instructed not to change any other medications during the study. **Outcome measures:** At the beginning of the study, after 2 weeks, and then at the end of the 4-week trial, parents completed the Conners' Parent Rating Scale — revised, long version, a questionnaire that assesses a broad range of problem behaviours (and was used as an indication of ADHD symptom severity). **Results:** After 2 weeks of treatment, the proportion of the subjects exhibiting improvement (i.e., decrease in T-score of at least 5 points) ranged from 31% for the anxious-shy attribute to 67% for the psychosomatic attribute. After 4 weeks of treatment, the proportion of subjects exhibiting improvement ranged from 44% for the social problems attribute to 74% for the Conners' ADHD index and the DSM-IV hyperactive-impulsive attribute. Five (14%) of 36 subjects reported adverse events, only 2 of which were considered related to the study medication. **Conclusions:** These preliminary results suggest AD-FX treatment may improve symptoms of ADHD and should encourage further research on the use of ginseng and *Ginkgo biloba* extracts to treat ADHD symptoms.

**Objectif :** Un produit à base d'herbes médicinales combinant 200 mg d'extrait de ginseng américain (*Panax quinquefolium*) et de l'extrait de ginkgo (50 mg) (AD-FX; CV Technologies, Edmonton [Alb.]) a fait l'objet d'essais pour vérifier sa capacité d'améliorer les symptômes du trouble d'hyperactivité avec déficit de l'attention (THADA). **Conception :** Étude ouverte. **Patients :** 36 enfants de 3 à 17 ans répondant aux critères de diagnostic du THADA. **Interventions :** On a administré pendant quatre semaines des

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gélules d'AD-FX deux fois par jour aux enfants sur un estomac vide. On avait demandé aux patients de ne changer aucun autre médicament pendant l'étude. **Mesures des résultats** : Au début de l'étude, après deux semaines, puis à la fin de l'essai de quatre semaines, les parents ont rempli la nouvelle version longue de l'échelle de notation parentale de Conners, un questionnaire qui vise à évaluer un vaste éventail de problèmes de comportement (et qu'on a utilisé pour préciser la gravité du symptôme de THADA). **Résultats** : Après deux semaines de traitement, la proportion de sujets présentant une amélioration (c'est-à-dire une diminution d'au moins cinq points de la note T) est passée de 31 % chez ceux qui connaissaient un problème d'anxiété-gêne, à 67 % chez ceux qui affichaient un symptôme psychosomatique. Après quatre semaines de traitement, le pourcentage de sujets présentant une amélioration est passé de 44 % chez ceux qui montraient des problèmes sociaux, à 74 % en ce qui concerne l'indice THADA de Conners et le symptôme d'hyperactivité-impulsivité dans le DSM-IV. Cinq (14 %) des 36 sujets ont signalé des événements défavorables, dont deux seulement ont été considérés comme liés au médicament à l'étude. **Conclusions** : Ces résultats préliminaires laissent entendre qu'un traitement à l'AD-FX est susceptible d'améliorer les symptômes du THADA et qu'il y aurait lieu de favoriser d'autres études sur l'utilisation d'extraits de ginseng et de ginkgo pour le traitement des symptômes du THADA.

## Introduction

Attention-deficit hyperactivity disorder (ADHD) is a condition characterized by developmentally inappropriate inattention and impulsivity, with or without hyperactivity.<sup>1</sup> The prevalence of ADHD in school-age children has been reported to be 5%–10%, and it is responsible for about 50% of the referrals to childhood diagnostic clinics.<sup>2</sup> Although previously considered to be an unusual disorder outside of Western society, the prevalence rates of ADHD in some developing countries with large urban populations may now be even higher than rates in North America.<sup>3</sup> The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), outlines 3 main subtypes of ADHD: predominantly inattentive, predominantly hyperactive and combined type.<sup>1</sup>

ADHD may place a child at risk for numerous challenges. If not properly managed, a child with ADHD will likely experience academic underachievement, increased risk of injuries and problems with self-esteem and socialization.<sup>4</sup> In adolescence and adulthood, those with ADHD are at risk for psychological disorders, substance abuse and addictions, traffic accidents and trouble with the law.<sup>5</sup>

Evidence suggests that the brains of those with ADHD differ both morphologically and metabolically from normal controls. One of the leading hypotheses suggests the behavioural and cognitive problems associated with ADHD may be explained, in part, by reduced polysynaptic dopaminergic neurotransmission in certain executive centres in the prefrontal cortex responsible for impulse control and the ability to maintain sustained attention.<sup>6,7</sup> Diminished dopaminergic

activity has also been implicated as a primary factor in the neurological basis for addiction.<sup>8</sup> In addition to morphologic differences and decreased dopamine reserves in prefrontal regions, memory deficits, commonly associated with ADHD, suggest that other brain regions, such as the hippocampus, and other neurotransmitters, such as acetylcholine, may be involved in ADHD symptoms.<sup>9</sup>

The prevailing approach to the treatment of ADHD is monotherapy with stimulant drugs such as methylphenidate (Ritalin), pemoline and dextroamphetamine (Dexedrine). In placebo-controlled trials, these medications successfully improved the behaviour and cognitive functioning of about 75% of the children treated with them.<sup>10</sup> Antidepressants may also influence dopaminergic activity, and several herbal extracts, including those from ginseng,<sup>11</sup> *Ginkgo biloba*<sup>12</sup> and *Hypericum perforatum* (St. John's Wort)<sup>13</sup> have also now been shown to increase cerebral dopaminergic activity. Intensive study of these and other agents is warranted.

### Ginseng extracts

Ginseng extracts have been widely studied in vitro and in animal studies. Of particular interest are the diverse effects that ginsenosides exert upon the central nervous system. These effects can be classified into 3 categories: nootropic, neurotrophic and neuroprotective. Nootropics are agents that facilitate learning, improve memory, promote attention, heighten sensory-motor performance and stimulate cognitive processing. Ginseng extracts have been shown to improve memory<sup>14,15</sup> and enhance learning by stimulating activity-dependent synaptic plasticity.<sup>16</sup> Ginsenosides have also been

shown to increase brain glucose utilization while simultaneously reducing lactate and pyruvate, indicating increased and more efficient aerobic metabolism within the brain.<sup>17</sup> In rodent models, ginsenosides have been shown to increase dopamine and norepinephrine levels in the cerebral cortex.<sup>18</sup> This may explain why ginseng extract has favourable effects on attention, cognitive processing, integrated sensory-motor function and auditory reaction time in healthy human subjects.<sup>19</sup>

Ginsenosides have been shown to possess neurotrophic effects. The ginsenosides Rb1 and Rg1 have been shown to potentiate the effects of nerve growth factor, which is a critical endogenous neurotrophic substance.<sup>20</sup> This suggests that long-term administration of ginseng extract may have the potential to promote the growth of underdeveloped brain regions in those with ADHD.

### Ginkgo biloba

*Ginkgo biloba* has neuroprotective effects in animal and human models,<sup>21,22</sup> and has been shown to possess neurotrophic potential. Rats that undergo traumatic motor nerve damage show more rapid reinnervation under the influence of ginkgo extract than untreated controls.<sup>23</sup>

Ginkgo has also been found to have significant cognition-enhancing or nootropic effects. It has been shown in numerous European trials<sup>25</sup> and in a recent North American trial<sup>25</sup> to effectively enhance memory and cognitive performance in subjects with dementia.<sup>24</sup> Ginkgo has also been shown to significantly improve memory and other cognitive functions in healthy adults.<sup>26</sup>

Ginkgo extract has been shown to affect several central neurotransmitter systems; it has been shown to reverse the reduction in 5-HT<sub>1A</sub><sup>27</sup> receptors and noradrenergic receptors in the aged rat.<sup>28</sup> Recently, it was demonstrated that ginkgo extract produces reversible inhibition of both MAO-A and MAO-B in the brain.<sup>29</sup> This mechanism may underlie the anxiolytic and mild antidepressant effects of ginkgo extract, and it may contribute to the improvement in the symptoms of ADHD seen in this study.

Given that ginseng and *Ginkgo biloba* extracts have diverse effects on the central nervous system and have the potential for influencing learning, memory and attention, it was of interest to determine whether AD-FX, which contains 200 mg American ginseng extract and 50 mg *Ginkgo biloba* extract in each capsule, could improve the symptoms of ADHD.

### Method

Children between the ages of 3 and 17 (mean age 10.2 years, standard deviation [SD] 3.7 years), who clearly matched the DSM-IV diagnostic criteria for ADHD, were recruited from several communities across Canada. The diagnosis of ADHD was confirmed by physicians before participants were initiated into the study.

Parents were carefully interviewed and asked to rate the severity of the DSM-IV inattentive symptoms their children displayed. Children who clearly exhibited at least 6 of 9 inattentive symptoms at a level of severity that was considered significantly disabling in at least 2 settings (generally school and home) were considered to fulfill the criteria for the "primarily inattentive" ADHD subtype. Children who clearly exhibited at least 6 of 9 hyperactive-impulsive symptoms at a level of severity that was considered significantly disabling in at least 2 settings were considered to fulfill the criteria for the "primarily hyperactive-impulsive" ADHD subtype. Similarly, those who clearly exhibited at least 6 of 9 significantly disabling symptoms in both the inattentive and hyperactive-impulsive symptom categories were considered to fulfill the criteria for ADHD "combined" subtype.

Children were excluded (not considered diagnosable) if they did not clearly exhibit some of these disabling symptoms before 7 years of age or if they had been previously diagnosed with a psychiatric disorder involving psychosis, any substance abuse disorder or a bipolar affective disorder. However, children were permitted to participate if they had been previously diagnosed with depression, obsessive-compulsive disorder or a learning disability.

In addition to fulfilling the DSM-IV diagnostic criteria for ADHD, children were only included in the study if their T-scores on the Conners' Parent Rating Scale - Revised (long version) (CPRS-R[L]; Multi-Health Systems Inc., Toronto, Ont.) were significantly elevated across several symptom scores.<sup>30</sup> The CPRS-R(L) questionnaire involves a multimodal assessment of a broad range of problem behaviours, such as conduct, cognitive, anxiety and social problems. The scoring system yields T-scores, which incorporate a large normative database adjusted for age and sex, on 7 individual symptom categories and 7 global categories. Improvement is defined as a change in individual symptom or global scores of at least 5 points toward the normal range of behaviour appropriate for that age group and sex.

To participate, parents and children had to be willing

to comply with all requirements of the study. If a child was on medication for ADHD when the study began, they were encouraged to avoid changing medication or dosage until the study ended. Children who were on medication were only permitted to participate if the symptoms of ADHD were poorly controlled in spite of medication. All participants were monitored for adverse events to evaluate the safety of AD-FX administration, alone and in combination with other agents.

All parents signed an informed consent form before

**Table 1: Individual reported adverse events after AD-FX administration**

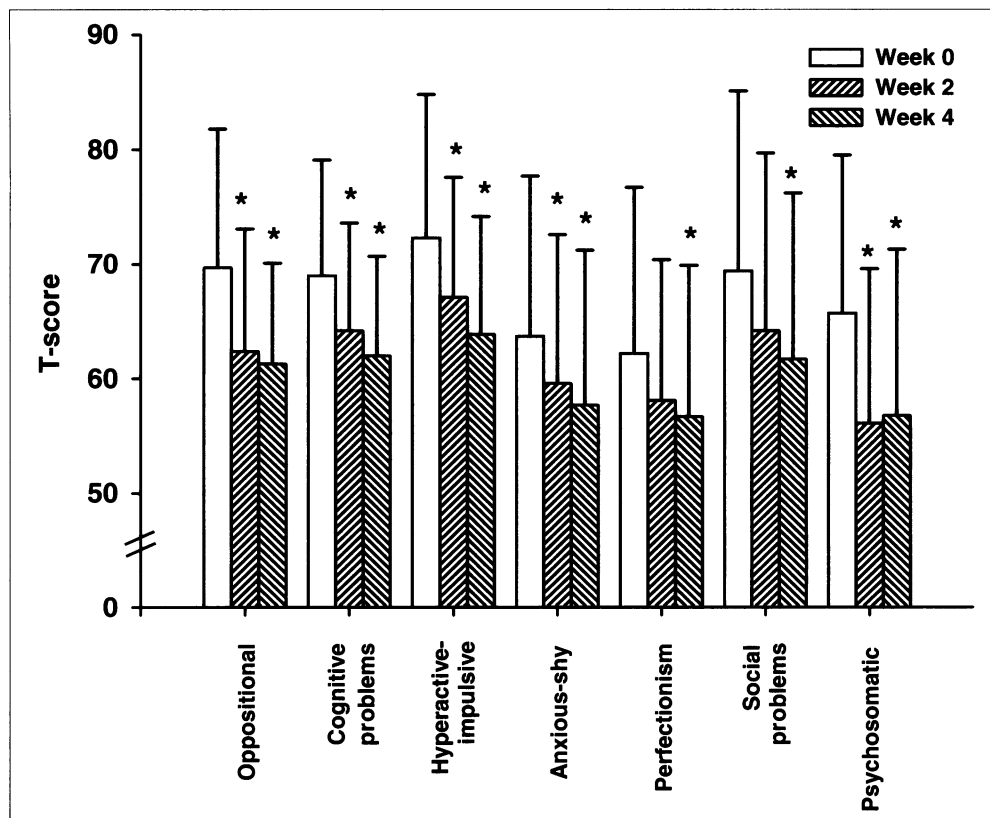
Adverse event	Product related?	Concomitant medications
More emotional, more impulsive	Yes	None
More hyperactive, more aggressive	Yes	None
Sweating	Uncertain	Ritalin
Headache	Uncertain	Ritalin
Tiredness	Uncertain	None

the study was initiated and completed the 80-question CPRS-R(L) as a baseline measure of ADHD symptom severity. Labelled bottles containing 60 capsules (a 4-week supply) of the herbal product AD-FX (HerbTech brand manufactured by CV Technologies, Edmonton, Alta.) were then distributed to the parents. The capsules contained 200 mg of North American ginseng extract *Panax quinquefolium* and 50 mg of *Ginkgo biloba* extract. Parents were instructed to give their child 1 capsule twice per day on an empty stomach (at least a half an hour before meals).

At the end of 2 weeks and again at study termination (4 weeks), parents were asked to complete the CPRSR-(L). Pretreatment baseline T-scores (week 0) were compared with T-scores for weeks 2 and 4. The T-scores were then analyzed for significant differences, with  $p < 0.05$ .

## Results

A total of 36 children were initially enrolled in the



**Fig. 1: Average T-scores for each of 7 symptom areas assessed using the Conners' Parent Rating Scale - Revised (L) (CPRS-R[L]). The results are means (and standard deviations) for 36 (0 and 2 weeks) and 34 (4 weeks) respondents. \*Significantly different from controls,  $p < 0.05$ .**

study — 14 from British Columbia, 16 from Alberta, 2 from Ontario and 4 from Quebec. Questionnaires were completed for all 36 children before they started taking AD-FX and again at 2 weeks; 34 questionnaires were completed after 4 weeks. Of the 36 subjects, 25 were taking other medications concomitantly (Ritalin,  $n = 9$ ; Dexedrine,  $n = 4$ , Efamol,  $n = 2$ ).

Five (14%) of 36 subjects reported adverse events over the course of the study (Table 1). The adverse events were considered to be related to the study medication in 2 cases. Interestingly, both of these subjects showed improvement on many of the ADHD symptoms; neither subject was taking concomitant medication.

The mean baseline T-scores were well within the range classified as “moderately atypical”<sup>30</sup> for each attribute. After 4 weeks, there was a significant improvement (i.e., reduced average T-score) exhibited on all of the 7 symptom categories for ADHD (Fig. 1).

After 2 weeks, 18 (50%) of the 36 children had improved on the hyperactive-impulsive attribute, 20

(56%) had improved on the cognitive problems attribute and 23 (64%) had improved on the oppositional attribute (Table 2). After 4 weeks, the corresponding number of children showing improvement were 22 (65%) of 34 on hyperactive-impulsive, 18 (53%) on cognitive problems and 21 (62%) on the oppositional attribute.

On all 7 global attributes of the CPRS-R(L), there was a significant improvement (i.e., significant reduction in mean T-scores) at 2 and 4 weeks (Fig. 2 and Table 2). The DSM-IV inattentive attribute was reduced by at least 5 points in 14 (39%) of 36 children after 2 weeks and in 18 (53%) of 34 after 4 weeks; at 2 weeks, 22 (61%) and at 4 weeks, 25 (74%) children had improved on the DSM-IV hyperactive-impulsive attribute. The Conners’ Global Index restless-impulsive attribute had improved for 19 (53%) of 36 children after 2 weeks and 18 (53%) of 34 children after 4 weeks.

In this small pilot study, it is difficult to establish whether there were any notable differences between

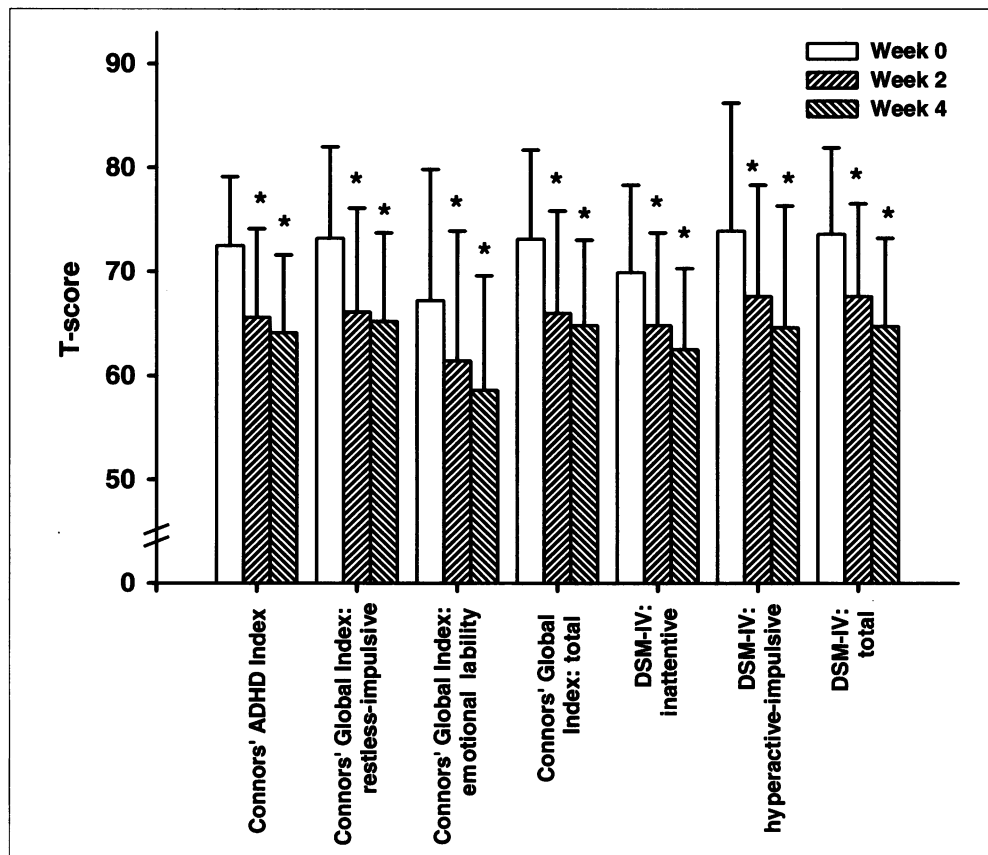


Fig. 2: Average T-scores for each of 7 global attributes assessed on the CPRS-R(L). The results are means (and standard deviations) for 36 (0 and 2 weeks) or 34 (4 weeks) respondents. \*Significantly different from controls,  $p < 0.05$ .

outcomes for subjects taking concomitant medications and those taking AD-FX alone (Table 3).

## Discussion

Our results indicate that the mixture of standardized extracts of American ginseng and *Ginkgo biloba* in AD-FX may significantly improve the symptoms of ADHD, as quantified using the CPRS-R(L). In all attributes examined there was a significant improvement, and in each of the 3 areas that are most troublesome in ADHD (i.e., hyperactivity, cognitive problems and oppositional behaviour), at least 50% of the subjects responded favourably after 4 weeks on AD-FX. This suggests that children exhibiting varying degrees of the different symptoms of ADHD can respond favourably with AD-FX. Children also exhibited significant improvements in the global attributes, with response rates of at least 50%. Overall, the response rate was very high, considering that 26 of 34 (76%) subjects exhibited a decrease in T-score of at least 5 points and 18 of 34 (53%) exhibited a decrease of at least 10 points in at least 5 attributes after 4 weeks of treatment.

Although these preliminary results are very encouraging, it is recognized that there are certain limita-

tions associated with repeated use of the CPRS-R(L). Such tests administered by a family member have the potential for some "placebo effect," and any placebo effect might be expected to wane rather than wax at 4 weeks, compared with 2 weeks. Additionally, there is the potential for a "practice effect," whereby there is an attenuation of the responses on repeated administrations. For this reason, it will be important in the future to factor results obtained with the CPRS-R(L) with other diagnostic tools.

This study, although small and uncontrolled, should

**Table 3: Number of CPRS-R(L) attributes for which a 4-wk treatment with AD-FX, alone or with another medication, was associated with a decrease in T-score\***

Concomitant medication	No. of children	Avg. no. of attributes decreased by 5 points	Avg. no. of attributes decreased by 10 points
None	22	8	5
Dexedrine	3	7	5
Dexedrine and Ritalin	1	0	0
Efamol	2	11	7
Ritalin	7	9	7
Ritalin and clonidine	1	9	2

\*Decrease in T-score is assumed to be associated with an improvement of ADHD symptoms.

**Table 2: Number (and %) of subjects exhibiting positive changes, no change or negative changes in CPRS-R(L) T-scores for each attribute**

Attribute	No. (and %) exhibiting a positive outcome*		No. (and %) exhibiting no change†		No. (and %) exhibiting a negative outcome‡	
	2 weeks	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks
<b>Part A</b>						
Oppositional	23 (64)	21 (62)	11 (31)	11 (32)	2 (6)	2 (6)
Cognitive problems	20 (56)	18 (53)	14 (39)	15 (44)	2 (6)	1 (3)
Hyperactive-impulsive	18 (50)	22 (65)	14 (39)	11 (32)	4 (11)	1 (3)
Anxious-shy	11 (31)	16 (47)	21 (58)	15 (44)	4 (11)	3 (9)
Perfectionism	16 (44)	16 (47)	15 (42)	14 (41)	5 (14)	4 (12)
Social problems	13 (36)	15 (44)	20 (56)	14 (41)	2 (8)	5 (15)
Psychosomatic	24 (67)	20 (59)	11 (31)	10 (29)	1 (3)	4 (12)
<b>Part B</b>						
Conners' ADHD Index	21 (58)	25 (74)	15 (42)	9 (26)	0 (0)	0 (0)
CGI: restless-impulsive	19 (53)	18 (53)	15 (42)	14 (41)	2 (6)	2 (6)
CGI: emotional lability	20 (56)	19 (56)	11 (31)	12 (35)	5 (14)	3 (9)
CGI: total	23 (64)	20 (59)	11 (31)	13 (38)	2 (6)	1 (3)
DSM-IV: inattentive	14 (39)	18 (53)	20 (56)	14 (41)	2 (6)	2 (6)
DSM-IV: hyperactive-impulsive	22 (61)	25 (74)	11 (31)	8 (24)	3 (8)	1 (3)
DSM-IV: total	17 (47)	20 (59)	17 (47)	14 (41)	2 (6)	0 (0)

Note: CPRS-R(L) = Connors' Parent Rating Scale (revised, long version), CGI = Connors' Global Index.

The percentages for the 2-week outcome are for 36 respondents, those for the 4-week outcome are for 34 respondents.

\*Positive outcome is defined as a decrease in T-score for the attribute of at least 5 points.

†No change is defined as a T-score for the attribute within 5 points of the week 0 value.

‡Negative outcome is defined as an increase in T-score for the attribute of at least 5 points.

provoke interest in further studies of these and other promising botanical agents through more formal trials. In the past decade, there has been increased attention on the pharmacology and clinical utility of botanical extracts and derivatives to treat neurological, behavioural and psychiatric disorders. In Europe and Asia, and more recently in North America, as methods of standardization have improved and the safety and efficacy of botanical derivatives has been increasingly demonstrated, several herbal extracts are being more commonly used for these and other conditions.<sup>31</sup> Standardized extracts from the leaves of the *Ginkgo biloba* tree and from the root of various species of ginseng (*Panax* spp.) have received much attention in the scientific literature, perhaps because of their long history of use by various ethnic groups and because of their array of apparent benefits.<sup>32</sup>

Overall, there is mounting evidence to justify the use of ginseng extract in combination with *Ginkgo biloba* extract to enhance brain function. Because of their diverse mechanisms, these agents might provide significant benefits in the management of ADHD. To our knowledge, this pilot study is the first attempt to use a combination of these agents to manage symptoms of ADHD. Although the magnitude of responses might be less than desired (since there was a lot of variance), it is possible that a subgroup of this population exhibited a more dramatic benefit.

Our results suggest that AD-FX is safe and well tolerated and may help to effectively manage behavioural and cognitive difficulties experienced by children with ADHD. However, due to the subjective nature of parental assessment, as well as the absence of controls in this study, it is not possible to draw any definitive conclusions. A well-controlled trial of at least 10 weeks duration with rigorous clinical endpoints should be undertaken in the future.

## References

- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 4th edition (DSM-IV). Washington: The Association; 1994.
- Wolraich M, Hannah J, Pinnock T, Baumgaertel A, Brown J. Comparison of diagnostic criteria for attention-deficit hyperactivity disorder in a county-wide sample. *J Am Acad Child Adolesc Psychiatry* 1996;35:319-24.
- Wang Y, Chong M, Chou W, Yang J. Prevalence of attention deficit hyperactivity disorder in primary school children in Taiwan. *J Formos Med Assoc* 1993;92:133-8.
- Brooks R. Children at risk: fostering resilience and hope. *Am J Orthopsychiatry* 1994;64:545-53.
- Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 1993;150:1792-8.
- Barkley R. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull* 1997;121:65-94.
- Levy F. The dopamine theory of attention deficit hyperactivity disorder (ADHD). *Aust N Z J Psychiatry* 1991;25:277-83.
- Nash JM. Dopamine system may be the key to addiction. *Nature* 1997;386:827.
- Benezra E, Douglas V. Short-term serial recall in ADHD, normal, and reading-disabled boys. *J Abnorm Child Psychol* 1988; 16:511-25.
- Greenhill L. Pharmacologic treatment of attention deficit hyperactivity disorder. *Psychiatr Clin North Am* 1992;15:1-27.
- Itoh T, Zang Y, Murai S, Saito H. Effects of *Panax ginseng* root on the vertical and horizontal motor activities and on brain monoamine-related substances in mice. *Planta Med* 1989;55: 429-33.
- Ramassamy C, Naudin B, Christen Y, Clostre F, Costentin J. Prevention by *Ginkgo biloba* extract (EGb 761) and trolox C of the decrease in synaptosomal dopamine or serotonin uptake following incubation. *Biochem Pharmacol* 1992;44:2395-401.
- Butterweck V, Wall A, Lieflander-Wulf U, Winterhoff H, Nahrstedt A. Effects of the total extract and fractions of *Hypericum perforatum* in animal assays for antidepressant activity. *Pharmacopsychiatry* 1997;30(Suppl 2):117-24.
- Benishin C. Actions of ginsenoside Rb1 on choline uptake in central cholinergic nerve endings. *Neurochem Int* 1992;21:1-5.
- Sloley BD, Pang PKT, Huang BH, et al. Effect of oral administration of a ginsenoside-rich extract of American ginseng (*Panax quinquefolium*) on scopolamine-induced amnesia in a spatial learning task. *Eur J Pharmacol*. In press.
- Abe K, Cho S, Kitagawa I, Nishiyama N, Saito H. Differential effects of ginsenoside Rb1 and malonylginsenoside Rb1 on long-term potentiation in the dentate gyrus of rats. *Brain Res* 1994;649:7-11.
- Samira M, Attia M, Allam M, Elwan O. Effect of the standardized Ginseng extract G115 on the metabolism and electrical activity of the rabbit's brain. *J Int Med Res* 1985;13:342-8.
- Itoh T, Zang Y, Murai S, Saito H. Effects of *Panax ginseng* root on the vertical and horizontal motor activities and on brain monoamine-related substances in mice. *Planta Med* 1989; 55:429-33.
- D'Angelo L, Grimaldi R, Caravaggi M, Marcoli M, Perucca E,

- Lecchini S, et al. A double-blind, placebo-controlled clinical study on the effect of a standardized ginseng extract on psychomotor performance in healthy volunteers. *J Ethnopharmacol* 1986;16:15-22.
20. Himi T, Saito H, Nishiyama N. Effect of ginseng saponins on the survival of cerebral cortex neurons in cell cultures. *Chem Pharm Bull (Tokyo)* 1989;37:481-4.
21. Barkats M, Venault P, Christen Y, Cohen-Salmon C. Effect of long-term treatment with EGb 761 on age-dependent structural changes in the hippocampi of three inbred mouse strains. *Life Sci* 1995;56:213-22.
22. Garg R, Nag D, Agrawal A. A double-blind placebo-controlled trial of *Ginkgo biloba* extract in acute cerebral ischaemia. *J Assoc Physicians India* 1995;43:760-3.
23. Bruno C, Cuppini R, Sartini S, Cecchini T, Ambrogini P, Bombardelli E. Regeneration of motor nerves in bilobalide-treated rats. *Planta Med* 1993;59:302-7.
24. Itil T, Martorano D. Natural substances in psychiatry (*Ginkgo biloba* in dementia). *Psychopharmacol Bull* 1995;31:147-58.
25. Le BP, Katz M, Berman N, Itil T, Freedman A, Schatzberg A. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. North American EGb Study Group. *JAMA* 1997;278:1327-32.
26. Subhan Z, Hindmarch I. The psychopharmacological effects of *Ginkgo biloba* extract in normal healthy volunteers. *Int J Clin Pharmacol Res* 1984;4:89-93.
27. Huguet F, Drieu K, Piriou A. Decreased cerebral 5-HT<sub>1A</sub> receptors during ageing: reversal by *Ginkgo biloba* extract (EGb 761). *J Pharm Pharmacol* 1994;46:316-8.
28. Huguet F, Tarrade T. Alpha-2-adrenoceptor changes during cerebral ageing. The effect of *Ginkgo biloba* extract. *J Pharm Pharmacol* 1992;44:24-7.
29. White H, Scates P, Cooper B. Extracts of *Ginkgo biloba* leaves inhibit monoamine oxidase. *Life Sci* 1996;58:1315-21.
30. Conners CK. *Conners' rating scales — revised*. Toronto: Multi-Health Systems Inc; 1997.
31. Stoppe G, Sandholzer H, Staedt J, Winter S, Kiefer J, Ruther E. Prescribing practice with cognition enhancers in outpatient care: Are there differences regarding type of dementia? Results of a representative survey in lower Saxony, Germany. *Pharmacopsychiatry* 1996;29:150-5.
32. Hu S. A contribution to our knowledge of ginseng. *Am J Chin Med* 1977;5:1-23.