Oligomeric Proanthocyanidins (OPCs) for the Treatment of **Attention-Deficit/Hyperactivity Disorder**

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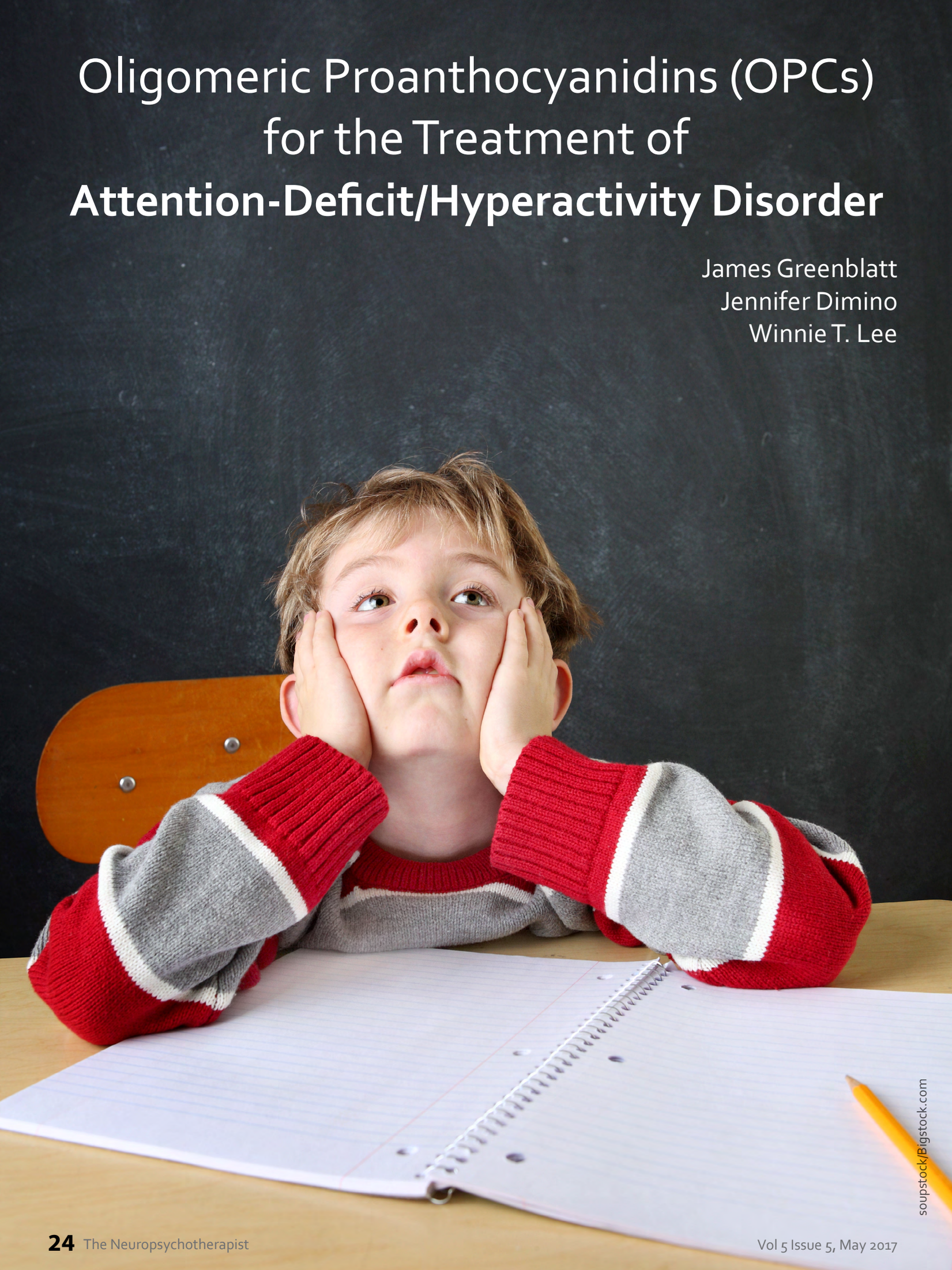

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It was 1534, and the crew of French explorer Jacques Cartier were in trouble. They had been ship-bound for months and surviving off meagre rations during their exploration of the eastern Canadian coastline for what would become the French empire's vast claims to North America. The inevitabilities of life at sea had caught up with them in devastating fashion: Cartier's men had scurvy. For many seafaring adventurers in that Age of Exploration, the cumulative effects of scurvy were intensifying and worsening preludes to a horrible disease, and often death. Vasco da Gama had lost two-thirds of his crew to scurvy in 1499, and in 1520, while attempting a trans-Pacific voyage, Ferdinand Magellan watched his ranks thin by 80% as scurvy claimed the lives of his men (Lamb, 2011).

However, it seems that luck was on Cartier's side, as he had befriended a tribe of Quebecois Native Americans in his explorations. Wise in the plant lore of their ancestors, they offered Cartier and his men a medicinal tea brewed from the needles and bark of special pine trees. To Cartier, the healing of his crew surely was not insignificant, and his journal entries are testament to the fact that this mysterious tea saved his men. The ramifications of the Quebecois' kindness also led to one of the most exciting breakthroughs in the field of nutritional psychiatry: the ancient wisdom of the Native Americans shared with Jacques Cartier in the 1500s has been shown by modern science to be an effective treatment for attention-deficit/hyperactivity disorder (ADHD).

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According to data from the Centers for Disease Control and Prevention (2017), an estimated 6.4 million children aged 4 to 17 are diagnosed with ADHD at some point in their lives, reflecting a 41% increase in the last decade alone. ADHD is characterized by an ongoing pattern of inattention and/or hyperactivity–impulsivity that interferes with an individual's functioning and development. Despite the thousands of scientific research papers published on the illness and diagnosis of ADHD, the etiology and treatment recommendations from medical and psychiatric professionals have changed little over the years.

The prevalence of ADHD today has given rise to widespread professional and public awareness, as well as a myriad of treatment approaches ranging from behavioral to pharmaceutical, while the concomitant surge in research churns out new scientific data that seem to upend every firmly held assumption on which these treatments have been based. Studies from around the globe are impressively united in their contradiction of the long-held belief that ADHD is a "kids' disorder". While ADHD typically manifests before puberty, new research has revealed that the disorder is lifelong, with prevalence rates amongst adults being nearly identical to those observed in children.

Perhaps most fascinating is the ongoing research exploring the genetic and biologic underpinnings of ADHD. While parents are primarily concerned with the behavioral manifestations of ADHD and strategies for symptom management, researchers have identified multiple biological changes associated with the behavioral and cognitive issues associated with ADHD. There is a growing body of unequivocal empirical evidence that validates ADHD as a neurologic, brain-based disorder represented by numerous biological abnormalities, so that what is observed as atypical behavior is merely the tip of a very large ADHD iceberg, the base of which can extend to an individual's genetic blueprint and biochemical makeup. A comprehensive list of the neurobiological changes that have been found to be associated with ADHD exceeds the scope of this article; however, a sampling of such a list would include the following:

- Several studies employing magnetic resonance imaging (MRI) technology have revealed abnormalities within the motivational circuitry of individuals with ADHD (Seymour, Reinblatt, Benson, & Carnell, 2015); neuroimaging studies have found unusual patterns of brain activation in individuals with ADHD, particularly within those networks involved in reward processing.
- A study examining the volume and quality of electrochemical signaling (communication) between brain regions found that ADHD children had atypical functional connections as compared with non-ADHD children (Costa Dias et al., 2013).
- Studies have revealed a genetic component to ADHD susceptibility; recent research investigating the incidence of ADHD amongst family members has yielded a heritability estimate of 76% in the general population (Faraone et al., 2005).
- Individuals with ADHD consistently display neurologic symptoms characteristic of insufficient dopamine. Dopamine plays a critical role in brain functions such as movement, attention, learning, and the reinforcing effects of many drugs. Researchers found that by administering a drug that enhances the release of dopamine in the brain of ADHD patients, symptoms were significantly relieved, thus confirming that ADHD symptoms are associated with insufficient dopamine (Carlson, 2014).

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- In our clinic, we have found many nutritional and metabolic disturbances related to the symptoms of ADHD, such as heavy metal toxicity, fatty acid imbalances, deficiencies of magnesium, iron, and zinc, and carbohydrate intolerance.

The emerging research on the pathophysiology and neurobiology of ADHD has consequently forced us to reexamine the ways in which we approach ADHD treatment. No longer can ADHD be thought of as a behavioral disorder. We now know that ADHD involves changes and functional abnormalities in specific brain regions,

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brain networks, biochemical processes, and even systemic metabolic processes. A disorder this complex requires a treatment approach that is equally multifaceted. Unfortunately, however, the reigning ADHD therapeutic paradigms utilized today are largely one-dimensional.

The administration of stimulant medications has long been the first-line treatment for ADHD, and drugs such as methylphenidate and dextroamphetamine are commonly prescribed to children as young as 3 or 4 years old to control restlessness, agitation, and impulsivity. By stabilizing dopamine levels in the brain, stimulants can affect an ADHD patient's scholastic performance and social functioning, and they have been successful at improving grades, self-esteem, and social relationships. Although the administration of pharmaceutical drugs treats the symptoms of the disorder, it fails to address the causes of ADHD. For some, the eradication of "problem behaviors" in the ADHD child is sufficient; yet stimulant medications may also carry a host of risks and negative side-effects including tics, insomnia, nausea and dizziness, as well as delayed growth, impaired vision, heart problems, and psychosis (Rubio et al., 2016).

The number of treatments available for ADHD can be overwhelming for patients and caregivers alike; these range from parent training, psychotherapy, medications, neurofeedback, and behavior therapy, some of which have been proven effective. Methods such as neurofeedback target imbalances and cognitive abnormalities that underlie adverse ADHD symptomatology.

Mounting empirical evidence demonstrates that OPCs are a safe, natural, and efficacious treatment strategy in supporting cognitive function in clients with ADHD.

If we return to the 1500s, we now know that Cartier's men were actually given a natural compound by the Quebecois that is found to have significant neurophysiological properties that improve symptoms observed in ADHD. These plant-derived compounds are known as oligomeric proanthocyanidins (OPCs), and while it may be premature for us to call them a miracle cure, mounting empirical evidence demonstrates that OPCs are a safe, natural,

Pine needle green tea

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and efficacious treatment strategy in supporting cognitive function in clients with ADHD. To the ADHD patient, practitioner or parent, OPCs are a beacon of hope, substantiated by modern science to effectively address many of the root biologic causes of ADHD.

A Brief History of OPCs

OPCs (i.e., oligomeric proanthocyanidins—sometimes known as proanthocyanidins or proanthocyanidolic oligomers), are a variety of polyphenol, a compound that plants produce as a defense against environmental harm. Polyphenol is a plant pigment that appears as red in cranberries, blueberries, and grapes; green in green tea; and the brown hue of dark chocolate. OPCs are also found in grapeseed, gingko biloba, plums, peaches, pine needles, and pine bark. For humans, the most beneficial molecular components of OPCs are flavonols, a type of antioxidant.

By the time Cartier and his men were introduced to the healing properties of pine tea, OPC-rich plant extracts had already been used as medicine in China and India for millennia. Between 1100 BC and 200 BC, Chinese physicians ardently supported the drinking of green tea (*Camellia sinensis*) to maintain health, and by the Tang Dynasty (AD 618–907), tea had become an object of medicinal veneration. According to practitioners of traditional Chinese medicine, green tea possesses cooling (yin) properties that help to refresh the mind, boost mental alertness, eradicate excess heat (yang), promote digestion, and relieve headaches. Passages from ancient Indian texts also demonstrate a rich history of using OPC-containing plants for therapeutic purposes: two plants that are prominently featured in Ayurvedic literature—*Cedrus deodara*, or Himalayan cedar, and *Pinus roxburghii*, or Indian longleaf pine—have been described as possessing central nervous system effects and have traditionally been used in Ayurvedic medicine to treat disorders of the mind (Chaudhary, Ahmad, & Mazumder, 2013).

In 1947, a French doctor by the name of Jacques Masquelier happened upon Cartier's journal, and became interested in the special properties of the pine tea that had been used to treat the explorer's company (Carper, 1998). As the needles of the pine used for the tea are rather low in vitamin C, Masquelier suspected another chemical was in fact responsible for saving Cartier's men (Passwater, 1991).

He was right: the pine needles and bark used to brew the scurvy-conquering tea were rich in OPCs. OPCs with small amounts of vitamin C had cured Cartier's crew of scurvy, and Masquelier promptly set out to learn as much as he could about this fascinating compound. He went on to extract OPCs from the skin of peanuts, and in 1950, OPCs derived from peanut skins were marketed as a blood-vessel protectant. Several years later, Masquelier discovered another rich source of OPCs in grape seeds. He was subsequently granted a patent for

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the extraction and medical application of OPCs in 1969 (Passwater, 1991).

Masquelier's work provided valuable insight for a possible explanation of the curious paradox concerning the epidemiological observation that French people exhibit lower incidences of coronary heart disease despite consuming a diet rich in saturated fats. Crediting the OPCs present in red wine, scientists found that OPCs exert multiple cardio-protective effects, as evidenced by their ability to decrease lipid peroxidation of low-density lipoprotein (Fuhrman, Lavy, & Aviram, 1995). Soon after this discovery, pharmaceutical companies developed drugs such as Endotelon to treat atherosclerosis and other cardiovascular diseases with OPCs from grape seeds as the active ingredient.

Today, OPCs are widely available to the public as a dietary supplement, with Pycnogenol most prominent among them. Pycnogenol is the registered trademark name of a nutritional supplement derived from *Pinus pinaster*, and is commonly used for treating circulation problems, asthma, tinnitus, high blood pressure, osteoarthritis, diabetes, female menstrual disorders, and retinopathy.

In keeping with the ancient traditions of Chinese medicine, Indian Ayurveda, and Native American plant medicine, OPCs show great promise as a nutritional biomedical therapy for ADHD. Based on observations spanning decades of clinical experience, OPCs can be incredibly useful in the treatment of ADHD for children and adults, either as an augmentation strategy for medications or as a stand-alone therapy.

OPCs as a Treatment for ADHD

A preliminary experiment conducted by psychologist Marion Sigurdson, involving 30 subjects with ADHD, found that attention and concentration (as measured by tests before and after the experiment) improved just as much with a daily regimen of pine bark-derived OPCs as with traditional ADHD stimulant medications (Carper, 1998). Additionally, the subjects reported experiencing better sleep and improved mood while taking the OPC supplement, corroborating centuries' worth of accumulated evidence from traditional systems of medicine that OPCs positively affect brain function.

Sigurdson's experimental outcomes were echoed in later research, including a randomized controlled trial seeking to investigate the effects of Pycnogenol on attention, oxidative DNA damage, and antioxidant status in ADHD patients and healthy controls. In a 2006 study, 61 children with ADHD aged 6–14 were randomly assigned to receive either Pycnogenol (1 mg/kg of body weight) or a placebo daily for one month, without any additional medications or supplements. Baseline measures taken at the start of the trial revealed that children with ADHD had significantly more oxidative DNA damage than their non-ADHD counterparts; after the study, markers of DNA damage were significantly lower in the group that had received Pycnogenol, even compared to measures taken from the non-ADHD controls (Chovanová et al., 2006). At the end of the study, children who had taken Pycnogenol displayed significantly elevated measures of antioxidant status. Within a month of discontinuing the supplement, however, subjects

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Gingko biloba

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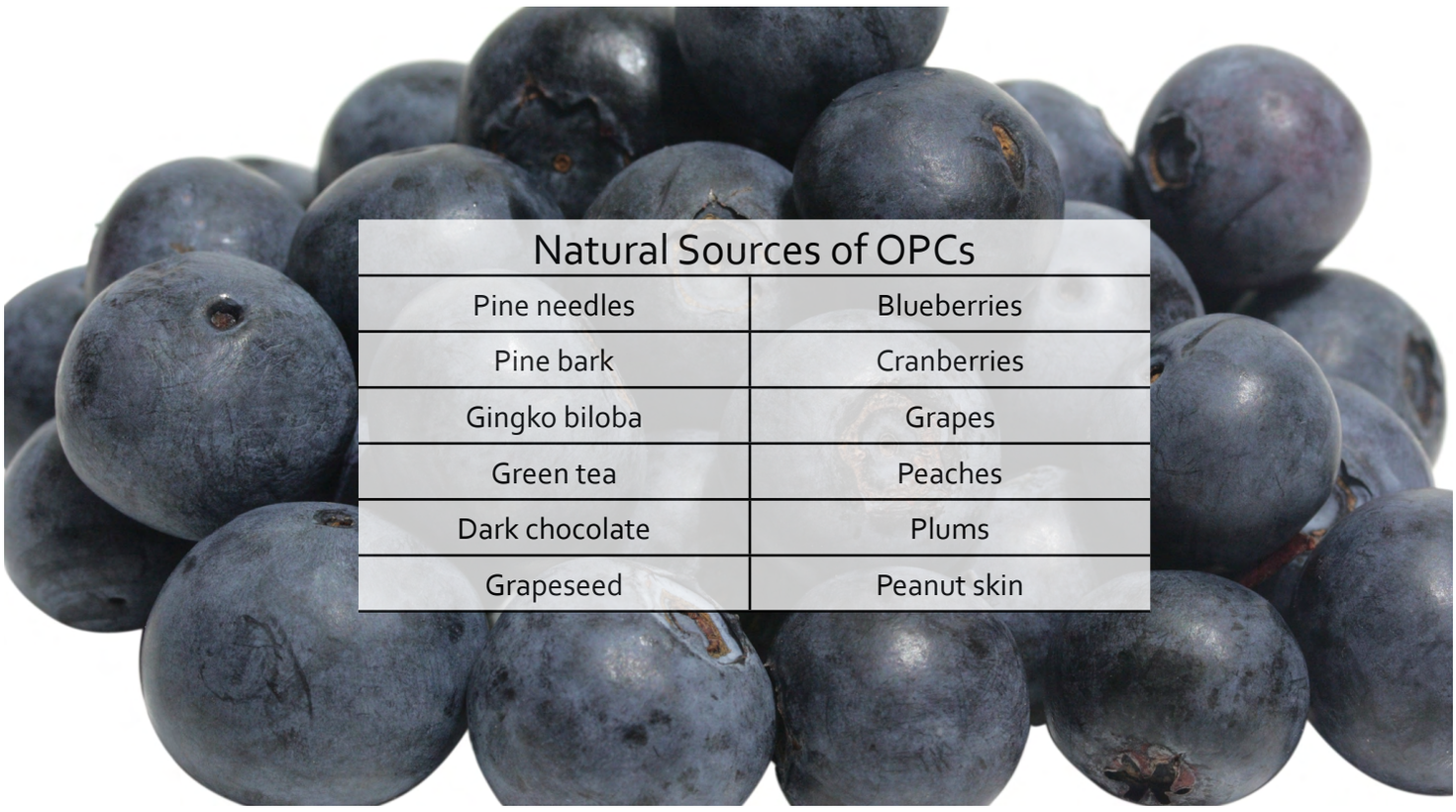
displayed increased levels of DNA damage. The data generated by this randomized controlled trial points to a strong association between DNA oxidation, total antioxidant status, and inattention.

Additional evidence in support of the efficacy of OPCs for ADHD comes from psychologist Dr. Steven Tenenbaum, who was diagnosed with ADHD as a child and lived with the disorder through adulthood. In addition to being a practicing clinical psychologist, Tenenbaum was an aviation enthusiast. Due to regulations of the Federal Aviation Administration, he was unable to utilize pharmaceutical treatments for his ADHD, and the use of stimulant drugs would cost him his pilot's license. He therefore turned to alternative therapies, and in 1995, initiated a regimen of Pycnogenol three times daily (Carper, 1998). According to Tenenbaum, the results were impressive: with Pycnogenol, he reported increased attention, improved focus, decreased emotional volatility, and elevated mood. Without Pycnogenol, Tenenbaum reported that ADHD symptoms would return immediately.

Tenenbaum's and Sigurdson's results with Pycnogenol supplementation are by no means unusual: numerous case reports, documented and anecdotal, have recorded substantial improvements in attention and focus, decreased restlessness and aggression, and emotional resiliency in ADHD patients who have been administered OPCs, and add to the body of literature supporting Pycnogenol supplementation as an alternative treatment for ADHD. For example, the case of a 10-year-old boy with ADHD, having experienced only marginal success on a regimen of stimulant drugs, was successfully treated with Pycnogenol was described in a letter to the editor of the *Journal of the American Academy of Child and Adolescent Psychiatry* (Heimann, 1999). The boy's parents noted significant improvements in his symptoms while the Pycnogenol regimen was maintained. When Pcynogenol was stopped, the boy experienced a significant exacerbation of ADHD symptoms.

The effects of OPCs have been tested in both ADHD patients and healthy, non-ADHD individuals, and the results from investigations into the latter are no less impressive than those of the former. For example, Luzzi et al. (2011) explored the effects of Pycnogenol on the cognitive abilities and emotional status of 53 healthy students aged 18–27. The students were tested before and after a regimen of Pycnogenol (100 mg/day) on measures of attention, memory, alertness, executive functioning, and mood, and showed significant improvements across-the-board after eight weeks of Pycnogenol supplementation. A more recent study from Exeter University (Bowtell, Aboo-Bakkar, Conway, Adlam, & Fulford, 2017) has documented the positive effects of drinking blueberry juice (rich in OPC flavonols) upon brain function in older adults. In this study, healthy participants aged 65–77 were randomly assigned to one of two experimental groups: members of the first group drank 30 ml/day of blueberry juice concentrate for 12 weeks, while members of the second group were given a placebo. Before and after the 12-week period, participants underwent a battery of cognitive tests while an MRI scanner monitored their brain function and resting



Natural Sources of OPCs	
Pine needles	Blueberries
Pine bark	Cranberries
Gingko biloba	Grapes
Green tea	Peaches
Dark chocolate	Plums
Grapeseed	Peanut skin

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brain blood flow. Compared to the placebo group, those who took the blueberry supplement showed improvements in cognitive function, working memory, blood flow to the brain, and brain activation while carrying out cognitive tests. Finally, a noteworthy study from the University of Reading examined the effects of blueberry extract consumption on cognition in children, and found that *every measure* of mental ability, including memory, improved in those children who drank blueberry extract (Whyte & Williams, 2015).

These data emphatically underscore what the wisdom from ancient Chinese, Indian, and Native American medical traditions has long recognized: OPCs can benefit the human brain, and powerfully enough to combat, minimize, and in some cases eliminate ADHD symptoms. Furthermore, OPCs can enhance cognitive performance, reduce anxiety, and improve mood in healthy individuals and ADHD sufferers alike. From the bark of the humble pine, the fruit of grape and blueberry plants, the fragrant leaves of green tea, and so many more abundant plant sources, we have a natural, plant-based therapy that may not only support those who struggle with ADHD but also large-scale approaches to the maintenance of general cognitive health.

Mechanisms of OPC Function

With regard to ADHD, there are a number of theories as to how OPCs work, and our understanding of how we can apply OPCs as targeted treatment therapies is still evolving. Current research has highlighted the potent antioxidant properties of OPCs and their ability to regulate neurotransmitter activity, stimulate neuronal growth, and reinforce immunological function.

Optimizing brain waves

Many studies have found that individuals with ADHD exhibit atypical electrical activity in the brain known as *cortical slowing*, which is the elevation of low-frequency theta waves and reduction of higher frequency beta waves in the prefrontal cortex. ADHD individuals tend to display significantly more theta activity (slow waves, 4–7 Hz) and reduced volumes of beta activity (fast waves, 13–31 Hz) as compared with the average non-ADHD individual (Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992). Theta waves are present during deep meditation and light sleep and have been negatively related to alertness. Beta waves in contrast are associated with normal waking consciousness, attention, and critical reasoning, and are responsible for completing executive functioning tasks.

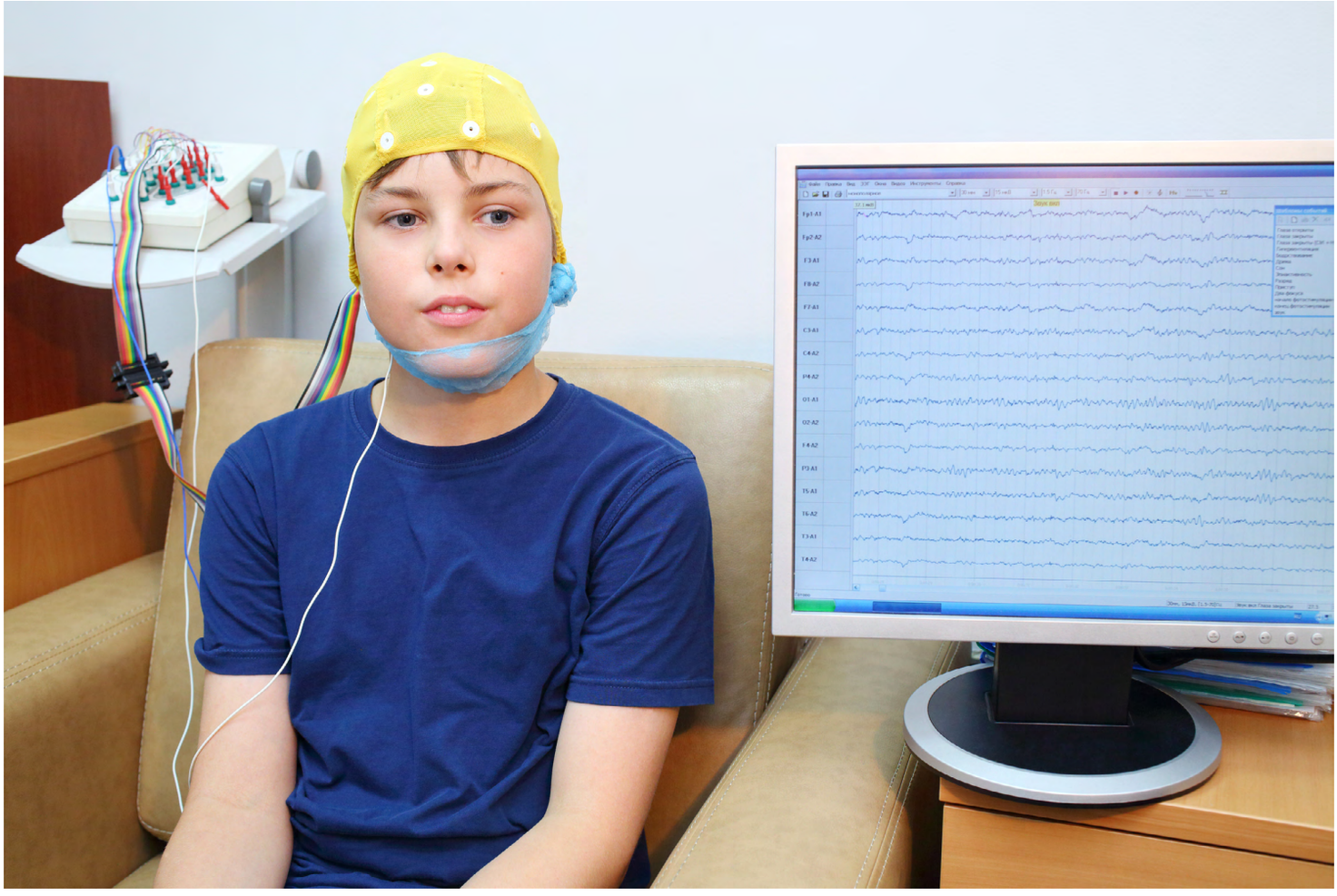
Neurofeedback is a nonpharmacological intervention that has shown promise in the long-term management of ADHD symptoms by teaching individuals to essentially change their brain wave activity. During neurofeedback training, clients receive feedback on their current brain activity and by using operant conditioning principles, clients can decrease theta activity and increase beta activity. The American Academy of Pediatrics has designated neurofeedback as Level 1 – Best Support, indicating that it is a safe, evidence-based treatment for childhood ADHD.

Several studies suggest that neurofeedback training is effective in stimulating cortical activation to decrease ADHD symptoms. By activating cortical function, it is hypothesized that new neural pathways and connections are activated, which may enhance the effects of pharmacological treatments (Toomim et al., 2004). When researchers compared the efficacy of neurofeedback in 131 students divided into four groups (neurofeedback group, pharmacological support group, combined group, and no-treatment group) and assessed participants' executive control and cortical activation pre- and post-treatment, the results indicated that the combined group reported more benefits and the neurofeedback group improved significantly in executive control than the pharmacological support group (González-Castro, Cueli, Rodríguez, García, & Álvarez, 2016).

A recent study from researchers at Tufts and Harvard Universities found that children who participated in neurofeedback had faster and greater improvements in ADHD symptoms, which remained at the six-month follow-up. Children were randomly assigned to receive computer attention training using neurofeedback, cognitive training, or a control condition three times per week over five months for a total of 40 sessions. Based on parental reports on multiple different rating scales, those in the neurofeedback group showed significant improvements over time compared with the control condition on inattention, executive functioning, and hyperactivity/impulsivity. In addition to parent reports, the neurofeedback group had significant improvements in off-task motor/verbal behavior compared with the control; the cognitive training group showed similar improvements (Steiner, Frenette, Rene, Brennan, & Perrin, 2014).

Neurofeedback has also been found to be as effective as medication in improving ADHD symptoms with long-lasting benefits. Some recent findings are:

- In one study, 130 ADHD children were randomly assigned to either neurofeedback or methylphenidate (Ritalin) or combined neurofeedback and



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medication, to compare the effectiveness of the three treatments on two core symptoms of ADHD: attention and hyperactivity (Duric, Assmus, Gundersen, & Elgen, 2012). Results indicated that neurofeedback was more than twice as effective in improving attention compared to the other two treatments, improved the core symptoms of ADHD, and was overall equivalent to the effects produced by methylphenidate (Duric et al., 2012).

- In another study, 23 children with ADHD were randomized to 40 theta/beta training sessions, or methylphenidate (Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013). Both treatments led to a similar reduction in ADHD functional impairment and in primary ADHD symptoms. However, only the neurofeedback group improved significantly in academic performance. These improvements were still seen at the six-month follow up (Meisel et al., 2013).

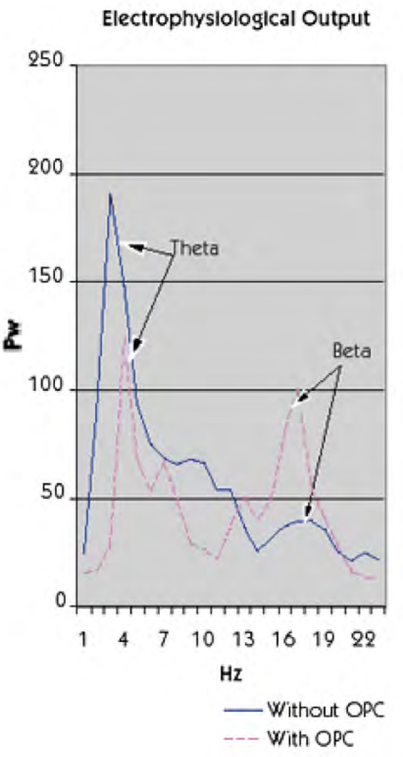

Figure 1. Electrophysiological output (pW) analysis of theta and beta waves by EEG: Following supplementation, theta wave output decreased and beta wave output increased on average for all tasks (baseline, reading, listening, and drawing) during EEG testing. Note the increased peak at 18 Hz following supplementation. Adapted from "Oligomeric Proanthocyanidins as an Alternative Treatment for ADHD" by J. M. Greenblatt, 2016, *Integrative Medicine for Mental Health*. http://www.integrativemedicineformentalhealth.com/articles/greenblatt_oligomeric_proanthocyanidins.html

Neuroimaging studies (via electroencephalogram/EEG) have confirmed the existence of irregular patterns of brain activation, impaired functional connectivity, and abnormal neurophysiology in ADHD individuals. It is logical, then, to presume that any intervention where multiple biochemical and/or imbalances of the brain are rectified would necessarily push the brain's electrical output towards the healthier side of the EEG spectrum, since improvements in neural output would manifest as increasingly normal brain waves. We have observed this phenomenon through OPC supplementation in our clinic.

Over the years, EEG analyses have been utilized with many of our ADHD patients. We have recorded multiple cases demonstrating EEG changes, handwriting changes, enhanced academic performance, improved behavior, and improved CPT (continuance performance testing) after supplementation with OPCs (Greenblatt, 1999). Prior to initiating the supplementation, we conducted baseline EEGs for individuals, and compared these baseline EEGs to EEGs following supplementation with OPCs (Figure 1).

Following OPC supplementation, patients have self-reported improvements in attention, focus, mood, and social interactions, and we have observed changes in their theta to beta ratios such that theta waves are reduced and beta waves are increased (Figure 2).

OPCs have profound effects on the brain systems and networks involved in attention and implicated in ADHD, as evidenced through data collected from multi-

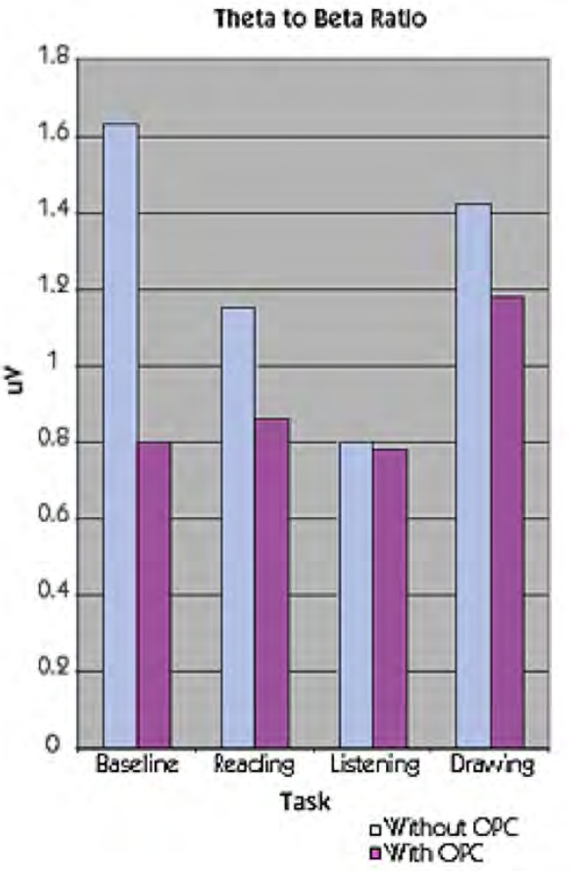

Figure 2. EEG analysis of theta to beta ratio during task performance: the change in theta to beta ratio (uV) for each task performed (baseline, reading, listening, and drawing) with and without OPC supplementation. Adapted from "Oligomeric Proanthocyanidins as an Alternative Treatment for ADHD" by J. M. Greenblatt, 2016, *Integrative Medicine for Mental Health*. http://www.integrativemedicineformentalhealth.com/articles/greenblatt_oligomeric_proanthocyanidins.html

ple EEG analyses in children and adults. The EEG changes, decreased theta waves and enhanced beta waves, are identical to what has been found with neurofeedback. However, neurofeedback can be expensive and time-consuming. While many individuals may require a multi-modal treatment plan, treatment as simple as supplementation with OPCs can be equally efficacious and improve patient compliance as well.

Copper and zinc balance

Trace minerals are critical to sustaining brain health and proper physical functioning and operate as essential cofactors in several enzymatic processes within the body. Zinc and copper are among some of the most actively studied minerals because they are required for the synthesis of neurotransmitters and play a key role in antioxidant defense against free radical damage.

As one of the most abundant trace minerals in the brain, zinc supports several critical neurologic processes, including supporting the growth of new neurons (Szewczyk, Kubera, & Nowak, 2011). Diets scarce in zinc have been known to manifest as behavioral disturbances and diminished brain function, and low serum plasma zinc levels have been associated with impairments in information processing and impulsivity in humans (Arnold & DiSilvestro, 2005). Lower plasma zinc levels have been consistently found among children with ADHD (Shin, Kim, Oh, Shin, & Lim, 2014). Zinc supplementation, therefore, has been researched for its utility as an adjunct treatment to standard pharmacologic therapies for ADHD. As an augmentation strategy, zinc has been successful at potentiating the beneficial effects of stimulant medications at lower dosages (Arnold et al., 2011), and a 2004 double-blind placebo-controlled study found that daily supplementation with 150 mg zinc reduced symptoms of hyperactivity and impulsivity, and improved social functioning skills in a group of children with ADHD (Bilici et al. 2004).

Zinc and copper have an antagonistic relationship, and multiple studies have confirmed the presence of abnormally high copper levels and correspondingly low zinc levels in both children and adults with ADHD (Russo, 2010). In excess quantities, copper competes with zinc for ligands (molecules that react with other molecules to form molecular complexes) and cellular transporters that are needed for absorption. Some receptor proteins on the surface membranes of cells are capable of recognizing and binding with either copper or zinc, hence key metabolic processes that depend on such receptors binding with zinc may be inhibited, as the copper will block zinc molecules from gaining access to the receptors.

An imbalanced copper to zinc ratio has resulted in a host of neurometabolic issues, such as accelerating the effects of oxidative damage to cells due to the oxidative potential of free-circulating metal atoms (Kodoma, Fujisawa, & Bhadh-

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prasit, 2012), and damaging essential neurotransmitter-producing nerve cells by destroying the cells' antioxidant defenses (Russo, 2010). Beyond being merely correlated with an ADHD diagnosis, irregular copper to zinc ratios have even been associated with symptomatic severity. A 2016 study investigating copper and zinc levels in 58 school-aged children with ADHD found that copper to zinc ratios were significantly correlated with instructor feedback regarding the students' inattention (Viktorinova et al., 2016). The students' poor attentional capacity was linked to quantitative findings regarding their abnormal copper and zinc levels, such that children with more abnormal copper to zinc ratios were found to have more serious inattention issues.

The relationship between copper and zinc is thus both dyadic and antagonistic: excess copper can deplete zinc levels, and zinc depletion can raise copper levels. As both minerals have been proven to mediate and/or moderate a host of processes that influence cognition, and irregular copper to zinc ratios have been linked by empirical research to disorders characterized by hyperactivity and impulsivity, it is unsurprising that we find such strong evidence tying high copper and low zinc levels to ADHD (Russo, 2010).

Based on this evidence, OPCs have been studied for their ability to chelate metal ions such as copper, with experimental research showing that OPC supplements can significantly decrease copper to zinc ratios in ADHD individuals. In a 2009 study, 65 children with ADHD aged 6–14 were randomized to receive either an OPC supplement or a placebo every day for four weeks. Compared to healthy controls, the ADHD children had lower zinc levels, higher copper levels, and higher overall copper to zinc ratios at baseline (Viktorinova, 2009). After a month, however, the ADHD subjects who had taken the OPC supplement displayed significant reductions in their copper levels, as well as their copper to zinc ratios.

Antihistamine function

A common denominator of neuropsychiatric diseases is a heightened inflammatory response. Children with ADHD have a much higher rate of immunoglobulin E-derived allergies than children without the disorder. They are also more likely to have ear infections, eczema, and asthma, all of which are forms of allergic responses. An overactive immune system results in systemic-wide inflammation.

OPCs may also help to regulate the production of histamine, an inflammatory biochemical secreted during allergic reactions that is correlated with ADHD symptom severity. Some children with ADHD possess a genetic mutation that disables their bodies from breaking down histamine, meaning they have stronger allergic reactions to triggers such as food dyes or artificial food additives. Severe allergic reactions can trigger an increase in the severity of ADHD symptoms. Thus, limiting histamine synthesis would represent a powerfully therapeutic modality for OPCs, and research suggests that this may indeed be the case.

Severe allergic reactions can trigger an increase in the severity of ADHD symptoms. Thus, limiting histamine synthesis would represent a powerfully therapeutic modality for OPCs, and research suggests that this may be the case.

OPCs are thought to slow the production and release of histamine from mast cells due to inhibition of the histidine decarboxylase, which is a required enzyme for the conversion of histidine to histamine (Dvoráková et al., 2006). This mechanism inhibits mast cell histamine release to dampen the body's allergic response. In recent years, a novel treatment approach has been studied for utilizing histamine H_3 receptor antagonists in neuropsychiatric disorders including ADHD and Alzheimer's disease, as they have shown pro-cognitive effects in preliminary animal studies (Schwartz, 2011). H_3 receptor antagonists are drugs that block the action of histamine at its autoregulatory H_3 receptors, which are mainly found on neurons within the brain. With this treatment, excess histamine within the cerebral cortex is now allowed to bind H_1 receptors and stimulate the release of excitatory neurotransmitters (glutamate and acetylcholine) within the central nervous system, and thus potentially improve attention and impulsivity.

Supporting the integrity of the blood-brain barrier

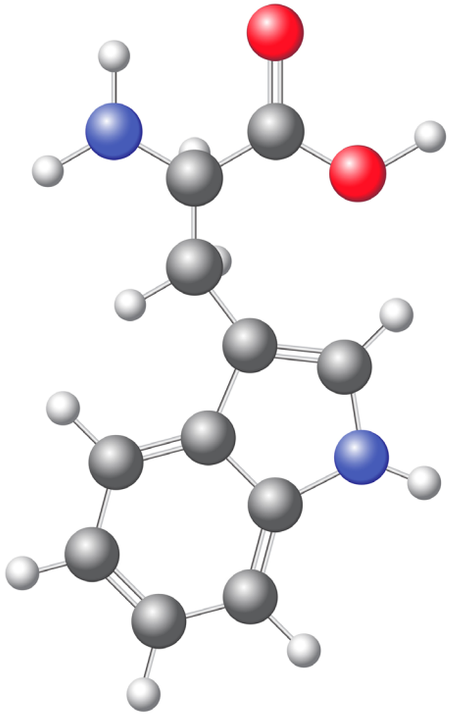
The blood-brain barrier (BBB) is a semipermeable "barrier" between the blood and brain that allows specific substances of a certain size and chemistry to pass through. The physical and functional integrity of the BBB is of paramount importance, as it determines which molecules gain access to the brain itself. A healthy BBB is therefore essential for the regulation of biochemical, neurotransmitter, and micronutrient levels within brain fluid, as well as for the protection of brain cells against substances carried within the blood that may be potentially damaging (e.g., toxins, pollutants).

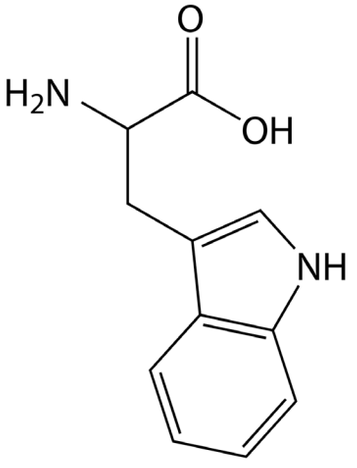
Unlike many other antioxidants, OPCs have a strong affinity for collagen–elastin crosslinks present within the tight junctions. This property allows OPCs to not only cross the BBB to have a positive effect on neuronal function, but also protect and maintain regulatory mechanisms present within the BBB. In vivo animal studies have shown that oral administration of OPCs can greatly increase the resistance of brain capillaries to the hydrolytic action of bacterial collagenases injected into their lateral ventricles, sustaining the collagen cross-linking component of the basement membrane (Robert, Tixier, Robert, Legeais, & Renard, 2001).

The BBB also helps maintain physiologic molecules from leaking out of the brain to maintain a proper homeostatic environment. Johansson and colleagues (Johansson et al., 2011) studied 14 boys with ADHD aged 6–12 years for deficiency in necessary brain chemicals. They found that levels of the amino acid tryptophan were almost 50% lower in ADHD patients than in normal brains and that alanine levels were much higher. Decreased transport of tryptophan due to a dysfunctional BBB can further lead to a deficiency in serotonin access in the brain that might cause disturbances in behavior and cognitive performance.

Maintaining the functional abilities of the BBB is integral to protecting the brain from penetrative harmful substances such as environmental toxins that can lead to oxidative damage within the brain. Over the past five decades, the use of synthetic food additives (i.e., artificial coloring) made from petroleum and preservatives (i.e., sodium benzoate) has increased by 500%. Children are consequently introduced to the greatest foreign antigenic load for challenging their immune system. These dyes are naturally small and therefore able to easily evade the host immune response. Additionally, they can bind body proteins to form immune complexes (antigen IgG) that are able to travel through an impaired BBB and deposit within the brain and/or peripherally mediate the release of histamine from mast cells and basophils.

A double-blind placebo-controlled food challenge was completed on 16 children and showed that on days with ingestion of reactive foods, their symptoms were significantly exacerbated when compared to placebo days (Boris & Mandel, 1994). Another study on 15 patients suffering from food-induced ADHD employed topographic (EEG mapping to show that intake of provoking foods directly increased brain electrical activity in the frontotemporal areas of the brain (Uhlig, Merkenschlager, Brandmaier, & Egger, 1997). In light of this measurable impact of food additives on ADHD patients, strictly supervised elimination diets may be used to provide valuable information regarding the cause of their ADHD.





Levels of the amino acid tryptophan were almost 50% lower in ADHD patients than in normal brains and alanine levels were much higher.

Decreased transport of tryptophan due to a dysfunctional BBB can further lead to a deficiency in serotonin access in the brain that might cause disturbances in behavior and cognitive performance.

Antioxidant function

OPCs possess powerful antioxidant properties that can serve to protect brain cells from oxidative damage by free radicals. The brain, which is comprised of lipid-rich neurons, is especially vulnerable to the negative effects of oxidative damage, and lipid peroxidation has been implicated in a host of neuropsychiatric diseases, including Alzheimer's disease and dementia. Many studies have alluded to the strong scavenging activity of OPCs which, in their oligomeric form (e.g., Pycnogenol), possess superior antioxidant activity to their monomeric counterpart and are a stronger antioxidant than both vitamin C and vitamin E. Additionally, this ability appears to be concentration-dependent, and when OPCs are combined with L-cysteine molecules, they exhibit even greater bioavailability, antioxidant activity, and survival time.

Neurotoxicity occurs when certain toxic chemicals (e.g., glutamate) lead to stimulation of N-methyl-D-aspartate (NMDA) receptor-mediated calcium influx into the cell mitochondria. Glutamate is an excitatory neurotransmitter present within the brain that becomes toxic when it accumulates in large quantities. A study in rats pretreated with OPCs found it was possible to partially dampen this excito-toxin-induced cascade by inhibiting the calcium signals within the neurons of the hippocampus region of the brain (Ahn et al., 2011). Another mechanism for protection against oxidative stress from lipid peroxidases, an enzyme that creates lipid peroxides, is by prevent breakdown of DNA within damaged tissue. Human studies have also demonstrated these antioxidant mechanisms, as evidenced by studies showing increased free-radical trapping capacity after consuming red wine rich in OPCs (Serafini, Maiani, & Ferro-Luzzi, 1998). OPCs have been utilized to actively absorb free metals before they produce these free radicals and potentially harm brain tissue.

Individuals with ADHD have vast changes in their oxidative metabolism and cellular immunity. This might also have a role in further understanding the causative etiology for their ADHD. In addition, many of these patients are often treated with standard pharmacological agents such as stimulants. Comim et al. (2014) demonstrated that rats given acute (1 day) or chronic (28 days) methylphenidate treatment experienced greater oxidative stress than controls due to decreased activity in enzymes that are responsible for removing free radicals. Overall, these findings suggest that supplementation with OPCs can effectively combat oxidative stress by enhancing antioxidant activity.

Individuals with ADHD have vast changes in their oxidative metabolism and cellular immunity.

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Stimulating brain-derived neurotrophic factor (BDNF)

While OPCs seem to limit or balance levels of neurochemicals that in excess can be damaging, they simultaneously appear capable of boosting the production of a certain chemical, brain-derived neurotrophic factor (BDNF), which is good for the brain. BDNF is a protein found in the central and peripheral nervous system. It plays an essential role in the growth, differentiation, and maturation of neurons, as well as developing and maintaining strong connections between neurons (Karege et al., 2002). Hence BDNF is a mediator of neuroplasticity, a term used to describe the brain's ability to reorganize itself in response to changing patterns of stimulation.

BDNF activity is crucial in supporting the brain's ability to respond to novel demands, such as learning new information, being stimulated in a new way, or even adaptively adjusting to compensate for damage. Experimental studies have shown that consumption of OPC-rich foods increases BDNF levels, which is critical for ADHD patients who might struggle with learning as a result of activational impairments in reward processing centers of the brain, or impaired electrochemical signaling between neural networks secondary to diminished functional connectivity (Takeda et al., 2011).

The proposed mechanisms of OPCs and their implications for health are summarized in the table below.

OPCs for ADHD

Science has demonstrated that OPCs directly benefit brain networks, neuron-to-neuron signaling, biochemical changes and metabolic processes that have been identified as underlying factors for many of the symptoms of ADHD. While it is speculative just how exactly OPCs improve cognitive function among individuals with ADHD, the available literature supports OPCs as a safe, naturally occurring, and therapeutic adjunct treatment that can improve cognitive performance and minimize the hallmark ADHD symptoms of hyperactivity and inability to focus. Their use as medicine over thousands of years is testament to their efficacy and safety, and modern research has corroborated that they are indeed effective and safe.

In over two decades of using OPCs to treat patients with ADHD, we have never observed any negative side effects associated with OPC supplementation. Instead, we have observed patients whose thinking becomes progressively clearer once they start taking OPCs. Countless patients have also reported an improved ability to concentrate and maintain focus, a steady improvement in their ability to read, write, and listen, and parents of patients have shared anecdotal stories about improvements in behaviors at home and performance in school.

The emerging research on the pathophysiology and neurobiology of ADHD is forcing us to reexamine the ways in which we approach ADHD treatment. Thanks to Jacques Cartier and Jacques Masquelier, OPCs are available to today's mental health professional to offer to his or her ADHD patient as a viable augmentation strategy for relief of their ADHD symptoms.

Mechanisms of OPCs and their implications for health

Properties and Mechanisms	Biochemical Action	Implications for Health
Balance brain waves	Improve theta to beta brain wave ratio	More focus and attention; less distractibility
Normalize mineral balance	Chelate (bind to and remove) copper, improving copper to zinc ratio	Improve antioxidant status, easing symptoms
Antihistamine / anti-inflammatory	Affect the expression of genes that regulate histamine and inflammation pathways	Inhibit inflammatory response, especially after consumption of artificial food ingredients
Strengthen BBB	Maintain integrity of tight junctions and strengthen blood vessels	Protect the brain from damage from free radicals and environmental toxins
Antioxidant properties	Destroy free radicals thus preventing oxidative stress	Reduce cell damage
Stimulate BDNF	Activate BDNF survival pathway	Increase the number, health, and survival of brain cells to learn new information

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