Therapeutic Approaches for Attention Deficit-Hyperactivity Disorder

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Abstract

Attention deficit-hyperactivity disorder (ADHD) is characterized by inattention, impulsivity, and hyperactivity symptoms that affect about 5% of children worldwide. ADHD pathology has been associated with the disruption in dopaminergic, serotoninergic, cholinergic, and adrenergic pathways. Currently used pharmaceutical agents effectively reduce the symptoms in the short term with various side effects and are not effective over long periods. Therefore, more interest has developed towards the development of drugs from natural products, including herbal medicines/phytochemicals. In Ayurveda, the progression of ADHD is curable when treated by using both the internal and external medications with a variety of therapeutic procedures, including Swedana (sudation), Snehan (oleation), Shodhana procedures like Virechana (purgation), Nasya, Lepa (external application), Dhumapana (medicated smoke), Vamana (emesis), Basti (medicated enema), Parisheka (oil bath), Anjana (Collyrium application), Abhyanga (massage), and Shamana Chikitsa (internal medication). In the Siddha medicinal text, ADHD symptoms have been associated to Sanni noi called

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Alathidu Sanni. A study indicated that the exposure of the ADHD child to various varmams nullified the symptoms and behavior. According to the traditional Chinese medicinal theories, ADHD can be treated using Chinese herbal medicine (CHM), with adjuvant acupuncture, tuina, tai chi chuan, and diet. A wide range of nutritional supplements such as vitamins, amino acids, essential fatty acids, and minerals were projected as possible adjuncts and alternative ADHD treatment strategies. Due to the multifactorial pathology of ADHD, the multi-therapeutic approach is needed to manage the disorder. Moreover, combined therapies involving both pharmaceutical agents and natural products/nutrients might also help improve the overall functioning by targeting the symptoms of ADHD.

Keywords

Attention deficit-hyperactivity disorder · ADHD · Natural products · Phytochemicals · Herbal medicine · Nutritional supplements · Pharmacological agents · Therapy

9.1 Introduction

Attention deficit-hyperactivity disorder (ADHD) is a behavioral and psychiatric disease affecting 5% of children worldwide. About 60% of cases persist into adolescence and adulthood stages. It is mainly characterized by invasive symptoms of inattention, impulsivity, and hyperactivity. It has been associated with conduct rebellious disorder, obsessive-compulsive disorder, personality disorder, depression, enhanced threat of obesity, autism, and epilepsy (Cabarkapa et al. 2019). In addition, children, adolescents, and adults with ADHD exhibit worse connection with family members; enhanced threat of accidental injuries; lower class performance; enhanced school denial and grade retention; earlier sexual commitment resulting in teenage pregnancy; addiction to marijuana, tobacco, and other drugs; reduced job performance; and increased psychological problems resulting in poor quality of life (Peasgood et al. 2016; Dalsgaard et al. 2015).

9.2 Anatomical Changes in ADHD

Neuroimaging studies indicated that the structural abnormalities in the cortex might lead to ADHD. Abnormal cortical development might be due to mitochondrial dysfunction, impaired energy, oxidative stress, inflammation, and apoptosis. Langleben et al. (2001) reported reduced flow of blood to the prefrontal cortex (PFC). In addition, structural abnormalities and alterations in their functions were found in the affected children. The main morphological aspect linked with ADHD was the structural thinning of the PFC and precentral area of the cortex. About 50% of the cortical thickness was attained in 7.5 years of normal-developing children, while the same was developed in 10-year-old ADHD children, indicating a

significant lack of cortical development. Children with ADHD showed a reduction in cortical volume due to diminished cortical folding and surface area, which worsened due to the aging process and drug intake.

Batty et al. (2015) indicated a significant decline in the volume of thalamus and dorsolateral PFC in ADHD children. They suggested that the pathological changes found in cortex development were linked with the maturation of thalamus. Apart from the cortex and thalamus, decreased striatum size (responsible for hyperactivity and memory) and a decline in the volume of the cerebellum (related to cognitive and affective function) were found in ADHD children (Hill et al. 2003).

9.3 Neurobiology of ADHD

In 1971, Wender was the first scientist who indicated that the abnormalities in the neurotransmission system could lead to the symptoms of ADHD. There are several neurotransmitters such as dopamine, noradrenaline, and serotonin that are reported to have a wide range of functions. Dopamine exerts key roles in the arousal, control of motor and executive functions, reinforcement, motivation, and reward by activating various signaling pathways by binding with the dopaminergic receptors found in the regions of the dopaminergic pathways of the human brain. Serotonin (5-hydroxytryptamine, 5-HT), an important neurotransmitter, is reported to be involved in mood, movement, social behavior, pain appreciation, endocrine secretions, sleep-wake cycle, cardiac outputs, and memory. Serotonergic neurons are mainly found in the raphe nuclei present in the medulla, pons, and a few regions of the brain stem, which extends primarily to the cerebral cortex and limbic areas. Noradrenaline is another neurotransmitter responsible for the arousal behavior (learning, pleasure, and anxiety) and activity of human beings. Noradrenergic neurons are present abundantly in the locus coeruleus nucleus of medulla and connected to the cerebral cortex and limbic areas by several pathways. ADHD has been associated with the disruption of dopaminergic, serotoninergic, cholinergic, and adrenergic pathways (Yuan et al. 2018).

9.4 Dopaminergic Hypothesis

Levy (1991) showed the relationship between the dopamine (DA) depletion in cortex and striatum and the ADHD symptoms, and proposed the dopamine theory of ADHD.

The dynamic developmental theory The malfunction of dopamine transmission in frontal-limbic circuits leads to lowered levels of tonic dopamine that results in a sharp and delayed reinforcement gradient and reduced extinction (Sagvolden et al. 2005). ADHD children tend to react superior to immediate rewards than delayed rewards.

Dopamine transfer deficit theory Although there is a presence of stimulant level of dopamine, the alterations of phasic dopamine response to reinforcement were found. Schultz (1998) indicated that there is a reduced transfer of dopaminergic signals from actual rewards to earlier actions that consistently envisage the future reward. The lack of reinforcement of attending by anticipation of dopamine release leads to inattention symptoms; that is, the children cannot pay more attention to information, commit careless errors, and neglect on-task behavior. Inadequate phasic dopamine response to rewards results in impulsivity (delay between the target behavior and actual reinforcement) and hyperactivity (children skip the seats in the classroom).

Four diverse proofs support the role of DA in the cause of ADHD as follows:

1. Data from experimental studies indicated that the symptoms of ADHD were linked with the alterations of the dopaminergic system in animals.
2. Support from pharmacological studies pointed out that the drugs used for the treatment of ADHD act in the DA system.
3. Evidence from brain imaging studies revealed that the patients showed problems in the brain regions having dopaminergic nerves.
4. Proof from genetic experiments indicated that alterations in the genes associated with the synthesis, transport, and degradation of DA were mainly found in the patients.

The facts that are against the strength of the dopamine hypothesis are as follows:

1. Psychostimulants and inhibitors of the noradrenaline transporter nullified the symptoms of ADHD.
2. The key discovery in ADHD is its linkage with polymorphism of the D4 receptor gene. However, few studies indicated that ADHD is a disorder raised due to defects in few regions of the brain.
3. There is also a possibility of dull dopamine responses in few ADHD patients even after the administration of methylphenidate due to higher baseline dopamine tone.

9.5 Serotoninergic Theory

Clinical and preclinical studies have indicated the role of serotonin in the inflection of impulsivity, attention, and hyperactivity symptoms. There is a connection available between the serotoninergic neurons of raphe nuclei and the dopaminergic neurons of midbrain regions (substantia nigra and central tegmental area). Further, the serotoninergic projections are also connected to the dopaminergic terminals of striatum, PFC, and nucleus accumbens. In dopamine transporter (DAT) knockout mice, without inducing the levels of dopamine, hyperactivity was inhibited after the administration of inhibitors of serotonin reuptake or precursors of this neurotransmitter, indicating the importance of 5-HT. Moreover, elevated brain serotonergic activity in ADHD children was measured by indirect methods, i.e., enhancement in

the levels of 5-hydroxyindoleacetic acid (metabolite of 5-HT) in the cerebrospinal fluid, diminished release of circulatory prolactin (hormonal secretion is regulated by 5-HT), and lowered levels of circulatory 5-HT and platelet imipramine H3 B_{max} (substance used for labeling serotonin binding). All the above experiments highlighted the key role of serotoninergic system in the pathophysiology of ADHD (Oades 2010).

9.6 Cholinergic Theory

As per the cholinergic hypothesis, the changes in the function of the nicotinic acetylcholine receptor (nAChR) may result in ADHD symptoms, which is relieved by the activation of the receptors. But till now, nAChR medications are not approved for the treatment of ADHD. However, both the clinical and animal studies indicated that the activation of nAChRs could improve the symptoms and recover the executive functions (Potter et al. 2014).

Levin et al. (2001) studied the role of a placebo, nicotine, methylphenidate (MPH), and their combined treatment in adult patients for 21 days. Variability in response time was found to be enhanced in nicotine alone, and nicotine- and methylphenidate-treated groups. A decline in depressive symptoms was found initially (15th day) in the nicotine and combination groups and finally (21st day) in MPH-treated individuals. Other studies by Conners et al. (1998) and Gehricke et al. (2006) indicated that the administration of nicotine nullified the problems in learning, difficulty in concentrating, and daydreaming/zoning out in most of the subjects. ABT-089, -418, and -894 and AZD-1446 and -3480 (agonists of α4β2 nicotinic receptors) were developed and tested for ADHD. Administration of ABT-089 improved the symptoms such as Clinical Global Impression-Severity (CGI scale), working memory, and impulsive responding in ADHD children (Wilens et al. 2006).

9.7 Pharmaceutical Agents

ADHD is connected with disturbances in the function of brain catecholamines. The therapeutic agents enhanced the brain catecholamine levels, thereby attenuating the symptoms of ADHD. The drugs are categorized into stimulants and non-stimulants. Methylphenidate and dextroamphetamine are the predominantly used stimulant drugs that mimic the structure of dopamine and norepinephrine, thereby restoring the catecholamine levels and correcting the underlying abnormalities during ADHD. Atomoxetine, antidepressants (bupropion, phenelzine, and imipramine), and norepinephrine-specific reuptake inhibitors are non-stimulant drugs (inferior to stimulants) that have also been demonstrated to enhance the brain catecholamine levels resulting in the improvement of behavior (Table 9.1).

Table 9.1 Major pharmacological agents employed in ADHD management

Medication	Mode of action	Symptoms managed	Disadvantages	Common side effects
Amphetamines (AMPH)	Due to their structural similarities, (1) amphetamines are transported by the dopamine (DA), serotonin (SE), and norepinephrine (NE) transporters, thus diminishing the reuptake of synaptic dopamine, serotonin, and norepinephrine; (2) they bind trace amine-associated receptor 1 (TAAR1), phosphorylate DAT, and internalize into neurons to stop internal transport of dopamine; (3) they also induce the release of these neurotransmitters from the vesicles of presynaptic neurons into the cytoplasm	Short attention span, impulsive behavior, and hyperactivity	Only cure the symptoms in 70% of adults and 70–80% of children	Headache, stomach discomfort, and higher blood pressure Other symptoms—Loss of appetite, weight loss, nervousness, and insomnia
Methylphenidate (MPH)	By binding with dopamine and norepinephrine transporters, the drug reduces the reuptake of these neurotransmitters	Excessive hyperactivity, impulsivity, and inattention	Reduced growth It can create bipolar illness or Tourette's syndrome	Loss of appetite, weight loss, jitteriness, irritability, sleep disturbance, stomach upset, constipation, and heartburn
Atomoxetine	By binding with norepinephrine transporter (NET), it inhibits NE reuptake in all regions of the brain except cortex As there is a very low expression of DAT found in	Slows down the hyperactivity and impulsive behavior, enhances the attention and concentration span	Data obtained on short-term use, whereas disadvantages of long-term use have not been assessed so far	Nausea, vomiting, insomnia, abdominal pain, reduced appetite, weight loss, headache, and sedation Dysmenorrhea, urinary retention, erectile dysfunction, and diminished libido in adults

	PFC, the reuptake of dopamine NET is stopped			
Extended-release clonidine	Induces adrenergic receptors (α2)	Has the calming effect and reduces the hyperactivity, impulsivity, aggression, overarousal, and sleep disorder Increases the day-to-day activity and performance	Unhelpful for inattentive symptoms Not suitable for treating adult ADHD patients	Dizziness, headache, vomiting, fatigue, dry mouth, and irritability Pain in upper abdomen, constipation Lowered blood pressure and erectile dysfunction
Extended-release guanfacine	Induces adrenergic receptors (α2)	Reduces the inattention and hyperactivity-impulsivity in ADHD youngsters	Not suitable for children with heart, hepatic, or kidney problems It can interact with other medicines such as phenytoin clonidine, rifampin, carbamazepine, ketoconazole, and valproic acid	Dizziness, headache, vomiting, fatigue, dry mouth, and irritability Pain in upper abdomen, constipation Lowered blood pressure and erectile dysfunction
Bupropion	Inhibits DAT and NET weakly	Minor improvement of ADHD symptoms	Insufficient evidence is present. More studies are required for confirming its therapeutic effect in adults and children	Headache, insomnia, gastrointestinal tract problems, body pains, chest pain, and dry mouth
Imipramine	Inhibits NET and serotonin transporter (SET)	Hyperactivity and impulsivity	As it is an antidepressant maximum efficacy is reached after 2–4 weeks	Nausea, dry mouth, drowsiness, and weakness Anxiety Changes in appetite
Modafinil	Inhibits DAT weakly than other psychostimulants	Treat symptoms of ADHD in adults 18 years of age and older	According to FDA, its use can be abused. The safety and effectiveness of children have not been established	Insomnia and decreased appetite Serious skin reactions

Disadvantages of pharmaceutical agents The pharmaceutical agents are effective in reducing the symptoms of ADHD for a short period, but not for more extended periods (Leucht et al. 2012). Few adverse effects, including drug abuse or dependency, might also occur. Safety is the major problem for a few patients, particularly those having cardiovascular disorders. The causes for discontinuation of drugs in the middle of the treatment include the apparent need for effectiveness, aversion during drug intake, and stigmatization. The choice of the drug for a specific patient is made on a trial-and-error basis, as the cause of ADHD is not fully known. Although these drugs improve ADHD symptoms (Ahn et al. 2016), 20–30% of affected individuals are nonresponders or unable to bear the side effects.

9.8 Traditional Therapeutic Approaches

Due to the adverse effects and lowered efficacy of current pharmacological drugs, research interests have developed towards the development of drugs from natural products including herbal medicines/phytochemicals (Bader and Adesman 2012; Searight et al. 2012). Since it is natural, complementary and alternative medicines are gaining attention by the caregivers. About 50% of caregivers choose these types of natural supplementations alone or in synergy with other drugs (Sinha and Efron 2005).

9.8.1 Ayurveda

Ayurveda has mainly accepted the undividable and inter-reliant relationship of sarira (body) and manas (psyche) and their individuality in humans. In Ayurveda, it is defined that the combination of body, soul, mind, and senses forms life. Acharya Charaka, the Ayurvedic text, narrates the "manas" as the entity that accounts for thinking. Ayurveda is the only ancient system of medicine that clarifies approximately all the behavioral and psychiatric diseases as Apasmara and Unmada. Unmada is described as the brain and psychiatric illness featuring uneven remembrance, mind, mental power, consciousness, and knowledge with bad manners (Shukla 2005).

Etiology The formation and development of the fetus (Garbha) are mainly dependent on the normalcy of Shonita (ovum) and Shukra (sperm). The lifestyle and diet of the pregnant lady are responsible for the normal growth and well-being of a child. Emotional instability such as excessive grief, fear, anger, and irritability; excess physical workload by brittle persons; control of natural urges; and unhygienic, improperly processed diet with irregular dietary habits are a few factors that affect the physical, mental, or both status of the baby and should be evaded by the pregnant women (Shukla 2005). The disturbance in the psychological factors and dietary patterns during the antenatal period would eventually affect the fetus and lead to psychological and neurobehavioral disorders. Depending upon the psychological

state of the parents, mana of fetus attains satwa, raja, and tama characters (Shukla 2005). Satwa Guna (positivity quality of mind) is likely to get diminished and this leads to Tridosha (three humors of body) that accumulates in Hridaya (heart/mental faculty), reducing the mental function and finally leading to Unmada (Gaud 2014).

The psychological problems arise due to an imbalance in the three humors that regulate the functions of body. Fear, insomnia, anxiety, and mental instability arise due to Vata imbalance; anger and irritability form due to Pitta imbalance, and depression and lethargy occur from Kapha imbalance (Sharma 2008). As Vata is the primary form of Tridosha that regulates the brain functions, their dysfunction results in hyperactivity. Children will be unable to control their stimuli and thoughts and will not be able to obey their parents or have fair activities. In most cases, Pitta dosha prevails over Vata dosha resulting in irritability, anger, not liking hot things or wearing clothes, and loving of cold air and water.

Treatment The progression of Unmada is curable by treating it with both the internal and external medications with a variety of therapeutic procedures including Swedana (sudation), Snehan (oleation), Shodhana procedures like Virechana (purgation), Nasya, Lepa (external application), Dhumapana (medicated smoke), Vamana (emesis), Basti (medicated enema), parisheka (oil bath), Anjana (Collyrium application), Abhyanga (massage), and Shamana Chikitsa (internal medication) (Kleigmn 2017). The preservation of Agni (digestive fire/metabolism) is done by using formulations such as Agnitundi Vati, Mustarishta, and Abhayarishta. It is of utmost importance, as in the absence of appropriate metabolism, actions of drugs can be unexpected. To manage the Vata and Pitta dosha, medicated ghee containing cognitive improvers (internal oleation therapy) and oil processed with soothing and cooling drugs (external oleation therapy) are used. As lipophilic agents can cross the blood-brain barrier, medicated ghee might act as a carrier for cognitive modifiers (Sharma 1990). The external oil massage stimulated the touch receptors and assisted in soothing the hyperactive children.

For treating Pitta-dominant disease, formulations such as Avipattikara Churna are the primary choice of drug. Virechana (purgation) is used to eliminate the accumulated metabolic wastes such as nitrogen compounds that may induce hyperactivity and aggressiveness in children. Basti is primarily used for Vata type of diseases by removing the toxins and preserving dosha balance. Acharya Charaka indicated that Rasayanas are reported to have compounds that maintain the brilliant quality of rasadidhatus (body tissues) that improve life span, inhibit aging processes, enhance intelligence, heal the disease, and build a strong and healthy body (Gaud 2014).

The drugs used to treat neurological diseases possess vatapitagna and kaphavatagna properties. Teekshna drugs such as Pippali (*Piper longum*), Twak (*Cinnamomum zeylanicum* Breyn.), Nidigdhika (*Solanum surattense* Burm.f.) and Vidanga (*Embelia ribes*), Bala (*Sida cordifolia*), Draksha (*Vitis vinifera*), Neelkamal (*Nymphaea stellate*), Manjishtha (*Rubia cordifolia*), Anshumati (*Desmodium gengeticum*), Swadanshatra (*Tribulus terrestris*), and Prapaundarika, (*Nelumbo nucifera* gaeris) have vatapitagna properties. Saindhava lavana (rock salt-potassium

chloride) (Sharma 2006), Madhuka (*Madhuca indica*), Rasna (*Pluchea lanceolata*), Brihati (*Solanum indicum* Linn), Twak (*Cinnamomum zeylanicum*), Nidigdhika (*Solanum surattense*), and Til oil (*Sesamum indicum*) containing drugs (Pandeya 2005) have Pittahara action and are used to diminish the Pitta-dominant symptoms like aggressive and agitated behavior.

9.8.2 Herbs

Bacopa monnieri (L.) Wettst. (B. monnieri) or Brahmi is an excellent cognitive enhancing Ayurvedic herb. More than 20 clinical trials studied the efficacy of Brahmi in children and adolescents with ADHD. Treatment with Bacopa improved the attention, cognition, intelligence, and behavior by altering sentence repetition, logical memory, delayed response learning, cognitive control, word recall (non-meaningful), digit span test, picture recall, and hyperactive and impulsive subscale in children and adolescents diagnosed with ADHD (Kean et al. 2016). Combination of Bacopa with *Centella asiatica* (primary ingredients), among few herbs, significantly improved the behavior compared to placebo in children and adolescents with ADHD (Dean et al. 2017).

Previous studies indicated that the daily administration of *Ginkgo biloba* extract (240 mg) led to modest improvements in the behavior (Uebel-von Sandersleben et al. 2014). In contrast, another study reported that the administration of the same extract (80–120 mg) showed an improvement in the teacher and maternal ratings of attention compared to placebo in ADHD children (Shakibaei et al. 2015). Another study compared the daily administration of methylphenidate (20–30 mg) with that of ginkgo extract (80–120 mg). Although the administration of methylphenidate is better than ginkgo, the side effects such as insomnia, diminished appetite, and headache were found in the former group as compared to ginkgo (Salehi et al. 2010). One study led by Niederhofer (2010) showed the beneficiary effect of St. John's wort, whereas another study by Weber et al. (2008) failed to nullify the symptoms in children with ADHD. Treatment of leaf extract of *Passiflora incarnata* (0.4 mg/kg/day) showed equal efficacy as methylphenidate (1 mg/kg/day) in improving symptoms without the adverse effects of methylphenidate (Akhondzadeh et al. 2005). Another clinical trial involving *Valeriana officinalis* root failed to show improvement in the children with ADHD (Razlog et al. 2012). Ayurvedic polyherbal medications such as Saraswat Churna, Saraswataghritha, Saraswatha Arishta, Manasamitra Vati, Brento syrup, Brahmivati, Memovit granules, Maha Kalyanaka Ghrita, Panchagavya Ghrita, Braintone syrup, and Shankhapushpi syrup provided better relief for ADHD.

9.8.3 Siddha

Siddha system is mainly practiced in South India and is an ancient traditional system of medicine. In this system, various modes of therapies such as varmam,

podithimiral, kombukattal, and thokkanam are available. Varmam is mainly used to treat numerous diseases that are linked with musculoskeletal and neurological problems. In the Siddha medicinal text, ADHD symptoms are connected to Sanni noi particularly called Alathidu Sanni, which is formed due to change in Vatham, Pitham, and Kabam. Varmam therapy is entirely anatomical and is regulated by Varmam treatment. A clinical study by Sasikumar et al. (2020) indicated that the exposure of ADHD children to Thilarthavarmamnatchathira varmam and Pidari varmam nullified the symptoms and behavior.

9.9 Traditional Chinese Medicines (TCM)

TCM is a broad medical system, followed for more than 2000 years. Although no specific name or diagnostic symptoms for ADHD are available in TCM literatures, the disease and their symptoms were depicted as injudicious behavior, forgetfulness, dysphoria, etc. According to TCM, it is a disease that affects emotion, thought, and mind. Yin controls calmness, while Yang controls movement; coordination is produced if the equilibrium between yin and yang occurs. According to yin-yang theory, both are conflicting and restricting, interdependent, and equally promoting each other. Both of them in the body are in balance, and their imbalance leads to diseases. The primary pathology lies in the disturbance of yin-yang, which results in the dysfunction of the Zang-fu (organs). The functions of theses 5 Zang-fu (liver, lung, kidney, heart, and spleen) are to synthesize and accumulate blood, qi, and other body fluids. The main functions of these organs are to maintain the mind and spirit. Ni et al. (2014) indicated that the TCM doctors recommend individual-based therapies for every patient, consisting Chinese herbal medicine, with adjuvant therapies like acupuncture, tuina (massage), tai chi chuan (breathing and exercise), and diet.

9.9.1 Chinese Herbal Medicine (CHM)

CHM formulae mainly consist of various herbs, minerals, and animal drugs that are utilized by TCM clinicians as therapeutic agents for ADHD. Treatment with Duodongning granule, a CHM containing Shudihuang (Rehmanniae radix preparata), Gancao (Glycyrrhizae radix et rhizoma), Renshen (Ginseng radix et rhizome), Wuweizi (*Schisandra chinensis*), Gouqizi (*Fructus lycii*), and Fuling (*Poria cocos*), offered a similar effect in hyperactivity, social performance, and academic success. The outcomes were similar to MPH (10 mg/day) treatment but with fewer side effects (Li and Chen 1999). Combined administration of Yizhi mixture (Guiban (Testudinis carapacis et plastri), Gouteng (Uncariae ramulus cum uncis), Shudihuang (Rehmanniae radix preparata), and Lujiaoshuang (Cervicornude gelatinatum) and Jingling oral liquid (Shanyao (Rhizome Dioscoreae)), Shichangpu (Rhizoma Acori Tatarinowii), Longgu (Os Draconis), Yuanzhi (Polygalae radix), and Shudihuang (Rehmanniae radix preparata) with MPH offered more

neuroprotective effect than the individual treatment because of their synergistic action with fewer side effects in ADHD children (Ding et al. 2002; Wang et al. 2011). Ningdong granule (Dangshen (Codonopsis radix)), Baishao (Paeoniae alba radix), Maidong (Ophiopogonis radix), and Tianma (Gastrodiae rhizome) treatment was more effective and safe than MPH treatment by increasing circulatory homovanillic acid concentration (increased dopamine metabolism) in ADHD children (Li et al. 2011). Ni et al. (2014) indicated that about 94 herbs are used as CHM formulae in 39 different studies for nullifying the symptoms of ADHD.

9.9.2 Acupuncture

Acupuncture (De-qi) is done by inserting fine needles (sterilized) at acupoints (particular body surface) followed by lifting, twisting, and rotating them to obtain the desired psychological effect responses. Acupuncture searches the meridian and controls the yin-yang and Zang-fu. Experiments by Chai (1999) and Shi (2002) indicated that the children with ADHD who received acupuncture showed a comparable effect as MPH in the short-term exposure. Further studies reported higher efficacy in long term with no side effects.

9.9.3 Tuina (Chinese Medical Massage)

It is a naturopathy process involving nonpharmaceutical and noninvasive methods such as rubbing, pushing, pressing, kneading, transporting, nipping, rotating, and foulage gently and delicately on specific meridians and acupoints. Tuina searches meridians, enhances qi and blood flow, fortifies the body resistance, and normalizes yin-yang. Wang and Shi (2005) applied tuina on the head, neck, chest, back, and abdomen of 33 children with ADHD. After 18 treatments, 10 children were cured, and 18 children showed significant improvement, while 5 had no effect. Another study by Zhuo (2006) compared the impact of tuina with MPH and indicated that both of them showed a similar effect, while tuina group demonstrated a reduced reappearance rate even 6 months after the treatment period.

9.9.4 Tai chi chuan (Breathing and Exercise)

Tai chi chuan (Taiji or tai chi) treatment is also an ancient form of TCM, which emerged 300 years ago. The underlying mechanism is balancing yin-yang and changing deficiency excess, which is also the basis for TCM. It involves the sluggish movements of active and stagnant forms. By moving, breathing, and exercising, Tai chi chuan induced and regulated qi and blood. By uniting deep, full, and shallow breathing with slow, gentle, and graceful movements, one can acquire inner rest and calm mind by transfer of the disturbing thoughts into attention.

Wen (2009) demonstrated that the ADHD children undergoing Tai chi chuan training program for 12 weeks showed reduction in symptoms of ADHD and improvement in vestibular function, learning abilities, and proprioception, as compared to the controls. Hernandez-Reif et al. (2001) observed that ADHD adolescents practising Tai chi chuan (two times a week for 5 weeks) showed improvement in hyperactivity, conduct disorder, anxiety, improper emotions, and daydreaming as compared to the control ADHD adolescent subjects.

9.10 Nutritional Supplements

Numerous nutritional supplements such as amino acids, vitamins, essential fatty acids, and minerals were projected as potential adjunct and alternative ADHD treatments.

9.10.1 Vitamins

Vitamins were used as probable adjuncts or substitutes for ADHD treatments because supplementation to normal children improved attention and concentration. Combination therapy of vitamin B6 with magnesium for 8 weeks enhanced the symptoms in ADHD children (Mousain-Bosc et al. 2006), which might be due to the synthesis of serotonin by vitamin B6. Another combination therapy involving vitamin C (antioxidant) and alpha-linolenic acid-rich flax oil (ALA, a precursor fatty acid needed for the synthesis of docosahexaenoic acid, required for the development of the brain) alleviated hyperactivity scores in ADHD patients (Joshi et al. 2006).

9.10.2 Minerals

Mineral deficiencies were reported to be involved in the cause of this disease. Therefore, supplementation might alleviate the ADHD symptoms. One clinical study involving the supplementation of zinc sulfate reported reduction in the symptoms of ADHD, while another study showed better efficacy and fewer side effects when compared to MPH. Few studies showed beneficial effect (Bilici et al. 2004; Akhondzadeh et al. 2004). Iron acts as a cofactor for the norepinephrine and dopamine biosynthesis, and anemic children are more prone to attention deficits. Few trials with iron supplementation offered beneficial effects, while others showed variable results in ADHD patients (Rucklidge et al. 2009). Another strategy involving the supplementation of all the minerals and vitamins improved the ADHD symptoms and mood due to their synergistic effect that affected the interrelated and defective biochemical pathways in ADHD patients (Rucklidge and Kaplan 2014).

9.10.3 Amino Acids

Numerous amino acids such as glycine, L-tyrosine, taurine, L-theanine, GABA, 5-hydroxytryptophan, acetyl-L-carnitine, and *S*-adenosyl-L-methionine acted as precursors for the synthesis of neurotransmitters. A study by Torrioli et al. (2008) reported that the supplementation of acetyl-L-carnitine significantly diminished the hyperactivity and poor social behavior in ADHD children by modulating neural transmission through elevated acetylcholine synthesis and stimulated the release of dopamine. Few experiments involving the supplementation of theanine, an amino acid available in green and black tea, revealed the positive effect on ADHD symptoms (Lardner 2014).

9.10.4 Essential Fatty Acids

Supplementation of essential fatty acid (EFA-omega-3 and 6) mixture of docosahexaenoic acid (DHA), γ-linolenic acid, eicosapentaenoic acid (EPA), vitamin E, *cis*-linoleic acid, arachidonic acid (AA), and thyme oil (Bloch and Qawasmi 2011; Sonuga-Barke et al. 2013) and a mixture of phosphatidylserine containing omega-3, EPA, and DHA (Manor et al. 2012) abolished the symptoms of ADHD. Few studies (Milte et al. 2012; Manor et al. 2012) indicated the beneficial role of EFA supplementation in ADHD, while others (Raz et al. 2009) showed controversial results.

9.11 Conclusions

Although there are numerous therapeutic options available for ADHD, few of them have adverse effects. Multi-therapeutic strategies are extremely prominent as they are more "suitable" and specific to each patient. Combination therapies involving both pharmaceutical agents and natural products might assist in improving the overall performance by nullifying the ADHD symptoms. Presently, only a handful of experiments were performed using this approach. More studies are needed in future to explore proof for long-term efficacy and safety.

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