A NUTRITIONAL APPROACH TO ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) MANAGEMENT- A REVIEW.

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ABSTRACT:
Nutrient deficiencies, such as vitamins, minerals, and polyunsaturated fatty acids, as well as dietary surpluses, such as sugar and artificial food additives, have not been proven to have a role in the genesis of ADHD. There is no solid data supporting dietary treatments for ADHD therapy at the group level. The complicated and ill-defined character of ADHD makes it difficult to identify a function for dietary components. Due to the disorder's variability, possible therapeutic advantages of dietary treatments may be limited to identifiable subpopulations of children with ADHD. In comparison to nutrient supplements, the combined advantages of the variety of foods that make up healthy diets may produce superior results. Diet and nutrition interact with other lifestyle factors like physical exercise, and research on treatment modalities for ADHD should place more emphasis on how diet and nutrition interact with lifestyle factors.

INTRODUCTION:

Attention Deficiency hyperactivity complaint(ADHD) is a neurodevelopmental illness that appears in immaturity as developmentally unhappy and disabled inattention, motor hyperactivity, and impulsivity, with difficulties that generally remain into majority.[1,2] Sir Alexander Crichton reported the condition for the first time around 1798. Despite the fact that ADHD exploration in the West was accelerating, a study addressing cases of hyperactive response in children was done for the first time in India in 1972, nearly 150 times after the complaint was first reported. It is described as "a harmonious pattern of inattention or hyperactivity-impulsivity that's more constantly expressed and more severe than is generally set up in persons of original experimental position." [3] It affects roughly 3 to 5% of children encyclopedically, with symptoms showing before the age of seven. ADHD is frequently a habitual illness, with 30 to 50% of people diagnosed in non- age still passing symptoms in maturity. Adolescents and grown-ups with ADHD are likely to acquire managing ways to compensate for their disability as they progress. youthful children in general are intolerant and energetic; the difference with ADHD is that symptoms appear over a longer period of time and in colourful surrounds. They've a negative impact on a child's capacity to perform socially, academically, and at home.

Signs and symptoms:-

It's natural for youths to have difficulty fastening and carrying at times. Children with ADHD, on the other hand, don't just grow out of these behaviours. The symptoms persist, might be severe, and can beget problems at academy, home, or with musketeers.
A child with ADHD might

- dream a lot
- forget or lose effects a lot
- fidget or twitch
- talk too important
- make careless miscalculations or take gratuitous pitfalls
- have a hard time defying temptation
- have trouble taking turns
- have difficulty getting along with others

Types:-

ADHD can manifest in three distinct ways, depending on which set of symptoms takes precedence in an individual:

1) Predominantly Inattentive Presentation: Individuals with this type struggle to organize or complete tasks, focus on details, or follow instructions or conversations. They are easily distracted and often forget routine activities.

2) Hyperactive-Impulsive Presentation: Individuals in this category exhibit restlessness, fidgeting, and excessive talking. Maintaining stillness for extended periods, such as during meals or homework, proves challenging. Especially in younger children, constant running, jumping, or climbing might be observed. Impulsivity is a key feature, leading to interruptions, inappropriate comments, and difficulty waiting their turn. This impulsivity might contribute to a higher frequency of accidents and injuries.

3) Combination Presentation: This form encompasses both inattentive and hyperactive-impulsive symptoms. The person experiences a balanced presence of inattentiveness and hyperactivity-impulsivity. This is the most commonly recognized type of ADHD, accounting for approximately 70% of cases.

It's worth noting that the presentation of symptoms can change over time, potentially leading to a shift from one type to another.[4, 5]

How ADHD is diagnosed?

While it's common for people to experience occasional lapses in attention, distractions, and impulsive behavior, those with ADHD tend to exhibit these symptoms more intensely and frequently. ADHD can have a negative impact on relationships, work performance, and self-esteem. Many adults with ADHD may not even realize they have it; they might simply struggle with everyday tasks. These behaviors can significantly affect their quality of life, whether at work, school, or home, if left untreated.[5]

According to CHADD, there isn't a single definitive test to diagnose ADHD. An accurate diagnosis requires a comprehensive assessment conducted by a trained professional, such as a psychologist, psychiatrist, pediatrician, or clinical social worker. This assessment aims to rule out other potential disorders and consider possible coexisting conditions.[6]

Medical professionals rely on the Diagnostic and Statistical Manual, Fifth Edition (DSM-5) published by the American Psychiatric Association for diagnosing ADHD. This standardized diagnostic criterion helps ensure accurate identification and appropriate treatment of individuals with ADHD. By using this consistent standard across communities, it becomes possible to determine the prevalence of ADHD among children and better understand its public health implications.[7]

Causes and risk factors:-

The causes and risk factors of ADHD are subjects of ongoing research aimed at developing more effective strategies to manage and reduce the likelihood of individuals developing the disorder. Although the precise causes and risk factors of ADHD are not fully understood, recent studies suggest that genetics plays a significant role. Current research has established a connection between genetic factors and the occurrence of ADHD. [3]

While the exact origins of ADHD remain elusive, factors such as genetics, environmental influences, and disruptions in the central nervous system during critical developmental stages are believed to contribute to its development. In addition to genetic predisposition, researchers are exploring other potential causative and risk factors, including:

- Traumatic brain injury
- Exposure to environmental hazards (e.g., lead) during pregnancy or early life
- Maternal alcohol and tobacco consumption during pregnancy
- Premature birth
- Low birth weight

Genetics:-

As per the aforementioned research published in the Lancet Psychiatry, there is evidence suggesting a hereditary component in ADHD, indicating a tendency for the condition to run in specific families. Although the specific genes associated with ADHD have not yet been pinpointed, the complexity of the disorder has led experts at the National Human Genome Research Institute to speculate that multiple genes might be implicated. These genes could potentially affect the functioning of neurotransmitters like dopamine, which plays a role in the brain's reward systems and the regulation of impulsivity and movement.

Exposure to environmental toxins and chemicals is another area of consideration:

Substance exposure, particularly to substances like lead, could potentially contribute to ADHD. Research has indicated a correlation between ADHD and blood lead levels. It's important to note, however, that while lead exposure has repeatedly shown a connection to ADHD, it isn't the primary cause of the condition, nor does it guarantee the development of ADHD in a child. Other environmental chemicals, such as bisphenol A (BPA) and phthalates, have also come under scrutiny for their potential impact on brain health, but no definitive link has been established between these chemicals and ADHD.

The impact of alcohol or tobacco use during pregnancy:

Studies have linked maternal tobacco use during pregnancy to ADHD symptoms in children. Nonetheless, recent research has raised questions about whether substance abuse directly causes ADHD. One study published in the Journal of Child Psychology and Psychiatry found no evidence that smoking during pregnancy contributes to ADHD. Another study, published in the International Journal of Epidemiology, suggested a potential modest link between alcohol consumption during pregnancy and reported ADHD symptoms, though not with clinical ADHD diagnoses. Despite this, pregnant women are still advised to avoid alcohol and smoking due to well-established risks like premature birth, low birth weight, and foetal alcohol syndrome.

The role of traumatic brain injury:

Early childhood traumatic brain injuries have been associated with the development of various mental disorders, with ADHD being the most prevalent among them. A report in

JAMA Paediatrics estimated that ADHD's prevalence in individuals with a history of traumatic brain injury is approximately 20%. Traumatic brain injuries are not uncommon, as millions of people seek emergency care for them annually.

Premature birth and low birth weight as potential risk factors:

According to certain studies, there appears to be a correlation between smaller birth weight or earlier delivery and a higher likelihood of developing ADHD. A meta-analysis and review of 34 studies, published in Pediatrics, supported this association, indicating an even stronger connection between very low birth weight or extremely preterm birth (before 28 weeks) and the development of ADHD.

Diet and behavioral factors:

Excessive sugar intake, food additives, and prolonged screen time (such as television, smartphones, tablets, and laptops) have been linked to ADHD. A small study published in BMC Pediatrics in January 2022 found that certain eating behaviors, particularly high sugar consumption, were more common in children with ADHD compared to those without the condition. However, while these factors may contribute to or exacerbate symptoms, there is no conclusive evidence that they directly cause ADHD. [8, 9]

Risk factors

While ADHD is not directly linked to other psychiatric or developmental conditions, children with ADHD are more susceptible than their peers to various disorders, including:

• Oppositional Defiant Disorder (ODD): This condition is characterized by a recurrent pattern of negative, defiant, and hostile behavior directed toward authority figures.

• Conduct Disorder: Marked by antisocial behavior such as theft, physical aggression, property destruction, and harming others or animals.

• Disruptive Mood Dysregulation Disorder: Individuals with this disorder exhibit impatience and struggle with managing frustration and emotional regulation.

• Learning Challenges: Difficulties with reading, writing, understanding, and communication may coexist with ADHD.

• Substance Abuse Disorders: Children with ADHD have a higher risk of developing issues with drug, alcohol, and tobacco use.

• Anxiety Disorders: Conditions like Obsessive-Compulsive Disorder (OCD) can result in excessive worry and unease.

• Mood Disorders: ADHD may also be accompanied by mood disorders such as depression and bipolar disorder, which involve periods of both depression and manic behavior.

• Autism Spectrum Disorder: This condition affects social interaction and communication, influencing how individuals perceive and engage with others.

• Tic Disorder or Tourette Syndrome: These conditions are characterized by involuntary and repetitive movements or vocalizations known as tics.[10]

POTENTIAL COMPLICATIONS OF ADHD:

Untreated ADHD can give rise to a range of long-term complications, encompassing:

• Poor Self-Esteem: Individuals with untreated ADHD may struggle with self-worth and confidence.

• Depression and Anxiety: ADHD can increase the risk of developing mood disorders like depression and anxiety.

• Eating Disorders: Some individuals with ADHD may be more prone to developing eating disorders.

• Sleep Issues: ADHD can disrupt sleep patterns and contribute to sleep problems.

• Substance Use Disorder: There is an elevated risk of substance misuse and addiction among individuals with untreated ADHD.

• Risky and Impulsive Behaviors: Impulsivity associated with ADHD can lead to engaging in risky behaviors without fully considering the consequences.

• Frequent Accidents and Injuries: Individuals with ADHD may experience more accidents and injuries due to their impulsivity and distractibility.

• Challenges in Relationships: Difficulties with social interactions can strain relationships with peers and others.

• Academic Underachievement: Unmanaged ADHD can lead to academic struggles and underperformance in school.

• Job Instability: In adulthood, untreated ADHD may contribute to challenges in maintaining stable employment.

CHALLENGES OF ADHD IN CHILDREN:

Children with ADHD face specific challenges, including:

• Academic Struggles: ADHD-related difficulties with focus and organization can lead to academic setbacks and criticism from peers and educators.

• Increased Accidents and Injuries: Children with ADHD are more prone to accidents and injuries compared to their peers without ADHD.

• Low Self-Esteem: Many children with ADHD experience low self-esteem due to their struggles and differences.

• Social Engagement Issues: Building and maintaining relationships with peers and adults can be challenging for children with ADHD.

• Risk of Delinquent Behavior: Children with untreated ADHD have a higher risk of engaging in delinquent behaviors, including alcohol and drug misuse.[11, 12]

Neurotransmitters:
The effectiveness of psychostimulants and noradrenergic tricyclics in treating ADHD highlights the role of neurotransmitters such as dopamine and noradrenaline in the disorder's pathophysiology. These medications work by enhancing the release and function of these neurotransmitters, suggesting that impaired neuronal transmission could be linked to the development and manifestation of ADHD symptoms. PET scans have revealed reduced dopamine activity in individuals with ADHD, reinforcing this association.[16]

Brain Structure:
ADHD is closely associated with specific brain regions, including the frontal and prefrontal areas, parietal lobe, and cerebellum. Magnetic resonance imaging (MRI) studies have demonstrated abnormal brain activity during specific tasks in children with ADHD [14]. Notably, structural anomalies in the basal ganglia nuclei have been observed, with greater deformities generally corresponding to more severe symptoms. The effectiveness of stimulant medications in mitigating these deformities lends support to this concept. Additionally, research indicates that children exhibiting higher hyperactivity and impulsivity tend to experience slower cortical thinning, particularly in the prefrontal regions, which is a characteristic pattern throughout adolescence.[14, 15]

Cognitive Function:
ADHD is associated with various neurophysiological deficits and cognitive abnormalities, often manifesting during resting states. Altered activity in the Default-Mode Network (DMN), responsible for processing self-related thoughts, may underlie the challenges individuals with ADHD face in regulating and sustaining attention. The involvement of top-down cognitive executive control becomes crucial for tasks involving memory, cognitive flexibility, and inhibition, especially during demanding activities requiring adaptability and exertion.[16]

ALLOPATHIC REMEDIES:

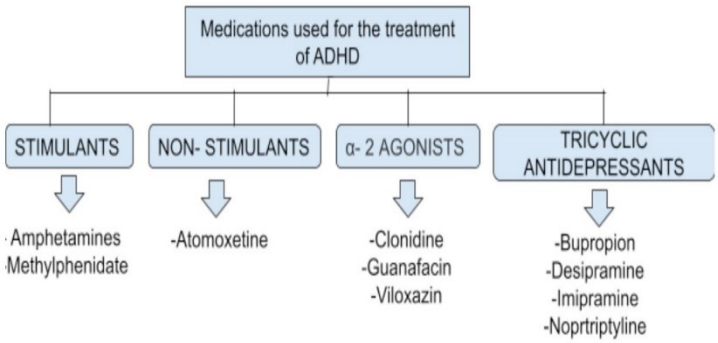
Effective treatment for ADHD often involves a combination of approaches, including medication, counselling, behavioural adjustments, and skill training. This comprehensive approach is referred to as multimodal therapy. Among the pharmaceutical options available, several are commonly used to address ADHD symptoms:

1. Stimulants: This class of medications has been a cornerstone of ADHD treatment for many years. Stimulants can aid in enhancing focus and reducing distractions. They prove beneficial for 70% to 80% of individuals with ADHD, ranging from mild to severe cases. Children, adolescents, and adults struggling with performance at school, work, or home can potentially benefit from stimulant medications. Some stimulants are considered safe for use in children as young as three years old, while others are recommended for those above six years of age.

2. Non-stimulants: When stimulants are ineffective or lead to undesirable side effects, non-stimulant medications can offer an alternative solution. These medications can help manage symptoms related to focus and impulse control.

3. Antidepressants: Many individuals with ADHD also contend with feelings of sadness, anxiety, or bipolar disorder. In such cases, healthcare providers may prescribe antidepressants to address these mental health challenges. In some instances, patients might receive both an antidepressant and a stimulant to address both their ADHD and other mental health conditions simultaneously. [17]

Remember, the optimal approach often involves tailoring treatments to individual needs, considering the specific symptoms and circumstances of each person with ADHD.



NUTRITIONAL MANAGEMENT FOR ADHD:

The significance of proper nutrition for the developing brain is underscored by the adverse impacts of malnourishment, including reduced DNA synthesis, cell division, myelination, glial cell proliferation, and dendritic branching. The brain's susceptibility to pathological effects due to nutritional deficiencies is contingent upon the stage of brain development during which the deficiency occurs[18]. Several instances of nutritional deficits and their developmental consequences are now well-established, such as iodine deficiency during perinatal stages, associated with preventable mental retardation globally[19], as well as folate deficiency linked to spina bifida and iron-related anemia. Profound shortages of omega-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA), can lead to significant cognitive impairment associated with peroxisomal disorders [20, 21].

ADHD and nutrition are interconnected through three principal mechanisms:

1. Adequate nutrient intake is essential for the proper function of brain cells, similar to other cells in the body.
2. The myelin sheath, akin to insulation on electrical wires, necessitates proper nutrition to facilitate effective transmission of electrical signals between brain cells.
3. Nutritional elements play a vital role in optimizing the functioning of neurotransmitters such as dopamine, serotonin, and norepinephrine.

The Role of Dietary Interventions in ADHD Management:
While there is no direct evidence linking nutrition to the behavioral disorder ADHD, dietary adjustments have demonstrated potential benefits for certain individuals in managing their symptoms. The impact of food and supplements on behavior has prompted substantial research into their effects on ADHD[3].

Micronutrients, encompassing minerals and vitamins, as well as polyunsaturated fatty acids (PUFAs), are prominent dietary components believed to offer potential therapeutic benefits for ADHD. Numerous studies have indicated lower blood plasma levels of specific minerals, including magnesium, iron, and zinc, in children with ADHD at a group level. Supplementation of these deficient minerals has been suggested to alleviate ADHD symptoms. However, conclusive evidence to substantiate these claims is lacking[22].

Research has explored various supplements' roles in addressing ADHD symptoms, ranging from PUFAs to individual micronutrients like zinc and vitamin D, as well as blends of micronutrients, herbal supplements, and probiotics.

Typically, two types of research methodologies have been employed:
1. Supplement Studies: Involving the addition of one or more nutrients to the diet.
2. Elimination Studies: Focusing on the removal of one or more dietary components[3].

Supplementation with Amino Acids:
The amino acids phenylalanine, tyrosine, and tryptophan play pivotal roles in the synthesis of neurotransmitters like dopamine, serotonin, and norepinephrine. Notably, individuals with ADHD often exhibit neurotransmitter imbalances and reduced levels of these amino acids in their blood and urine. Consequently, introducing these amino acids into the diet has shown marginal enhancements in the condition of ADHD patients.

Mineral and Vitamin Supplements:
Consistently lower levels of essential minerals such as zinc, magnesium, calcium, and phosphorus have been identified in children with ADHD. Addressing these deficiencies through dietary supplementation has yielded improvements in symptoms[3].

Zinc:
Beyond its critical involvement in immune function, growth, development, and reproduction, zinc significantly impacts brain development. Research by Arnold comprehensively explores zinc's role in brain function and its association with ADHD[23]. This investigation compiles findings from multiple global studies, all revealing diminished zinc levels in ADHD-afflicted children, further connecting lower zinc levels to the severity of symptoms. Fluctuations in

zinc levels have also been linked to exacerbations in behavioral and emotional symptoms among hyperactive children[24].

Iron:
Iron plays a vital role in the establishment and operation of the central nervous system, contributing to various neurotransmission processes. Insufficient iron levels have been associated with impaired cognitive development. It has been suggested that iron deficiency might impact cognition and behavior by influencing tyrosine hydroxylase, a rate-limiting enzyme in dopamine synthesis[25, 26]. The potential neuroprotective effect of iron against lead exposure has also prompted consideration of its relevance to ADHD[27].

Magnesium:
Suboptimal magnesium (Mg) levels can influence brain function through mechanisms encompassing decreased energy metabolism, synaptic nerve cell signalling, cerebral blood flow, and the nervous system's suppressive effect. This suppressive effect aids in the regulation of nervous and muscular excitability[28]. Decreased magnesium levels have been observed in children with ADHD.

Supplements for Omega-3 Fatty Acids:
Omega-3 fatty acids are vital for optimal brain function, with the brain, retina, and nervous system containing substantial levels of long-chain omega-3 PUFA docosahexaenoic acid (DHA)[29]. Children with ADHD often exhibit lower levels of omega-3 fatty acids compared to their non-ADHD counterparts. Notably, decreased omega-3 levels seem to correlate with increased learning and behavioral issues in ADHD individuals. Omega-3 supplementation has demonstrated potential in enhancing task completion, attention span, and reducing hostility, restlessness, impulsiveness, and hyperactivity. The role of omega-3 PUFAs in both the development and treatment of ADHD remains a subject of debate[30, 31]. Clinical studies have investigated the effects of omega-3 PUFA supplementation on ADHD symptoms due to significantly lower blood levels of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA) in children with ADHD compared to controls.

Herbal Supplements:

Pycnogenol and ADHD:
Antioxidants are gaining recognition for their potential to reduce oxidative stress in the brain, a factor associated with conditions like autism and ADHD[32]. Pycnogenol, derived from maritime pine bark, is a potent antioxidant rich in polyphenolic compounds such as procyanidins and phenolic acids[33]. Additionally, Pycnogenol has been noted to enhance blood circulation and increase nitric oxide production[34, 35], potentially aiding cerebral blood flow, which is impaired in ADHD.

Gingko Biloba:
Gingko biloba, a natural supplement, is believed to augment cerebral blood supply and inhibit platelet activation[36]. While comprehensive studies on its cognitive enhancement benefits are lacking, Gingko biloba has been marketed as a remedy for dementia and memory loss[37].

St. John's Wort (Hypericum perforatum):
This herbal supplement has been shown to inhibit the reuptake of serotonin, norepinephrine, and dopamine[38]. Its mechanism of action shares similarities with certain ADHD medications, like atomoxetine and bupropion[38].

Eliminating Artificial Colorants and Preservatives:
Studies have suggested a link between artificial colorants and preservatives (AFCs) and altered behavior in children, irrespective of ADHD diagnosis. One study involving hyperactive children indicated that 75% experienced improvement on an AFC-free diet, with symptoms returning upon reintroduction of AFCs. Another study involving 1,873 children found that AFCs and sodium benzoate, a preservative, exacerbated hyperactivity[3].

Reducing Sugar and Artificial Sweeteners:
Associations between sugary beverages and heightened hyperactivity have been noted. Individuals with ADHD often experience fluctuations in blood sugar levels, and observational studies have connected sugar consumption with ADHD symptoms in children and adolescents. The impact of sugar on attention is theorized to be related to blood sugar imbalances that lead to decreased attention levels[3].

CONCLUSION:
In summary, the efficacy of dietary interventions involving the supplementation or removal of specific nutrients in mitigating ADHD symptoms lacks conclusive evidence. The few-foods or oligoallergenic diet, however, serves as a diagnostic tool to identify children sensitive to certain foods. While this personalized dietary approach shows promise in alleviating ADHD symptoms, more robust empirical evidence is required. Dietary patterns are closely intertwined with the development and exacerbation of ADHD symptoms, with unhealthy eating habits being strongly associated and healthy diets inversely linked to the condition. Nutrients like vitamin D, iron, zinc, and PUFAs have been implicated in ADHD exacerbation and development. Thus, dietary interventions present a viable avenue for addressing ADHD. Nevertheless, more substantial empirical support is needed before these approaches can be fully integrated into ADHD treatment.

References:-

1. Nigg, J.T. Attention-deficit/hyperactivity disorder and adverse health outcomes. *Clin. Psychol. Rev.* **2013**, *33*, 215–228.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American Psychiatric Association: Arlington, VA, USA, 2013.
3. Vijayan V, Govind K & Raju R (2018). Managing ADHD with Nutrition – A Case Study Report. International Journal of Indian Psychology, Vol. 6, (2), DIP: 18.01.030/20180602, DOI: 10.25215/0602.030
4. Faraone, S. V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M. A., . . . Wang, Y. (2021). The World Federation of ADHD International Consensus Statement: 208 evidence-based conclusions about the disorder. Neuroscience & Biobehavioral Reviews. doi:10.1016/j.neubiorev.2021.01.022
5. American Academy of Child & Adolescent Psychiatry. ADHD & the Brain. *(https://www.aacap.org/AACAP/Families_and_Youth/Facts_for_Families/FFF-Guide/ADHD_and_the_Brain-121.aspx)*
6. Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD). ADHD — Overview. *(https://chadd.org/about-adhd/overview/)*

7. Attention-deficit/hyperactivity disorder. In: *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revision*. (DSM-5-TR™). Arlington, VA: American Psychiatric Association; 2022.
8. Obel C, Zhu JL, Olsen J, et al. The Risk of Attention Deficit Hyperactivity Disorder in Children Exposed to Maternal Smoking During Pregnancy — a Reexamination Using a Sibling Design. *Journal of Child Psychology and Psychiatry*. April 2016.
9. Eilertsen EM, Gjerde LC, Reichborn-Kjennerud T, et al. Maternal Alcohol Use During Pregnancy and Offspring Attention-Deficit Hyperactivity Disorder (ADHD): A Prospective Sibling Control Study. *International Journal of Epidemiology*. October 1, 2017.
10. ADHD. National Alliance on Mental Illness. https://www.nami.org/Learn-More/Mental-Health-Conditions/ADHD/Overview. Accessed Jan. 26, 2019.
11. Centers for Disease Control and Prevention. Attention-Deficit / Hyperactivity Disorder (ADHD). *(https://www.cdc.gov/ncbddd/adhd/index.html)*
12. Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD). ADHD — Overview. *(https://chadd.org/about-adhd/overview/)*
13. Wilens TE, Spencer TJ. Understanding attention-deficit/hyperactivity disorder from childhood to adulthood. Postgrad Med. 2010 Sep;122(5):97-109.
14. Barkley, R. A., Grodzinsky, G., and DuPaul, G. J. (1992). Frontal lobe functions in attention deficit disorder with and without hyperactivity: a review and research report. J. Abnorm. Child Psychol. 20, 163–188. doi: 10.1007/bf00916547
15. Miller E. K., Cohen J. D. (2001). An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 24, 167–202. 10.1146/annurev.neuro.24.1.167
16. Tannock R. (1998). Attention deficit hyperactivity disorder: advances in cognitive, neurobiological and genetic research. *J. Child Psychol. Psychiatry* 39, 65–99. 10.1017/s0021963097001777
17. Hansa D. Bhargava, MD; ADHD Medications and Side effects, March 9, 2021.
18. Lecours AR Mandujano M Romero G. Ontogeny of brain and cognition: relevance to nutrition research. *Nutr Rev*. 2001;59 (Suppl): S7– S11.
19. Hetzel BS. Iodine and neuropsychological development. *J Nutr*. 2000; 130 (Suppl): S493–S495.
20. Martinez M. Docosahexaenoic acid therapy in docosahexaenoic acid-deficient patients with disorders of peroxisomal biogenesis. *Lipids*. 1996; 31(Suppl): S145– S152.
21. Uauy R Peirano P Hoffman D Mena P Birch Birch E. Role of essential fatty acids in the function of the developing nervous system. *Lipids*. 1996; 31(Suppl): S167– S176.
22. Lange KW, Hauser J, Lange KM, Makulska-Gertruda E, Nakamura Y, Reissmann A, et al. The role of nutritional supplements in the treatment of ADHD: what the evidence says. Curr Psychiatry Rep (2017) 19:8. doi: 10.1007/s11920-017-0762-1
23. Arnold LE DiSilvestro RA . Zinc in attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2005;15:619–627.
24. Ward NI Soulsbury KA Zettel VH Colquhoun ID Bunday S Barnes B . The influence of the chemical additive tartrazine on the zinc status of hyperactive children – a double-blind placebo-controlled study. J Nutr Environ Med. 1990;1:51–57.
25. Black MM . Micronutrient deficiencies and cognitive functioning. J Nutr. 2003;133(Suppl):S3927–S3931.
26. Konofal E Lecendreux M Arnulf I Mouren MC . Iron deficiency in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med. 2004;158:1113–1115.
27. Konofal E Cortese S . Lead and neuroprotection by iron in ADHD. Environ Health Perspect. 2007;115:A398–A399.
28. Kozielec T Starobrat-Hermelin B . Assessment of magnesium levels in children with attention deficit hyperactivity disorder (ADHD). Magnes Res. 1997;10:143–148.
29. Salem N Jr Litman B Kim H-Y Gawrisch K . Mechanisms of action of docosahexaenoic acid. Lipids. 2001;36:945–959.
30. Lange KW. Dietary factors in the etiology and therapy of attention deficit/hyperactivity disorder. Curr Opin Clin Nutr Metab Care (2017) 20:464–9. doi: 10.1097/MCO.0000000000000415.
31. Lange KW. Do food bioactives play a role in attention-deficit/hyperactivity disorder? J Food Bioact (2018) 4:1–7. doi: 10.31665/JFB.2018.4160.
32. Ng F Berk M Dean O Bush A . Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int J Neuropsychopharmacol. 2008;21:1–26.
33. Rohdewald P . A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. Int J Clin Pharmacol Ther. 2002;40:158–168.
34. Fitzpatrick DF Bing B Rohdewald P . Endothelium-dependent vascular effects of Pycnogenol. J Cardiovasc Pharmacol. 1998;32:509–515.

35. Nishioka K Hidaka T Nakamura S , et al.Pycnogenol, French maritime pine bark extract, augments endothelium-dependent vasodilation in humans. Hypertens Res. 2007;30:775–780.
36. Arnold LE, Hurt E, Lofthouse N. Attention-deficit/hyperactivity disorder: dietary and nutritional treatments. Child Adolesc Psychiatr Clin N Am 2013;22(3): 381–402, v.
37. Canter PH, Ernst E. Ginkgo biloba is not a smart drug: an updated systematic review of randomised clinical trials testing the nootropic effects of G. biloba extracts in healthy people. Hum Psychopharmacol 2007;22(5):265–78.
38. Muller WE, Rolli M, Schafer C, et al. Effects of hypericum extract (LI 160) in biochemical models of antidepressant activity. Pharmacopsychiatry 1997; 30(Suppl 2):102–7.