

## Therapeutic use of omega-3, B complex vitamins, lutein, zeaxanthin for brain and eyes

- DHA helps maintain normal **brain function** and **vision** with a daily intake of 250 mg
- Normal psychological function, such as **learning and memory**, is maintained with the help of vitamins B<sub>3</sub>, B<sub>6</sub>, B<sub>12</sub>, biotin and folic acid.
- Vitamins B<sub>2</sub>, B<sub>3</sub>, B<sub>6</sub>, B<sub>12</sub> and folic acid contribute to the **reduction of tiredness and fatigue**
- Vitamins B<sub>6</sub>, B<sub>12</sub>, D<sub>3</sub>, folic acid and selenium contribute to the normal **function of the immune system**
- Maintenance of normal **red blood cells** is supported by vitamin B<sub>2</sub>, while their formation is supported by vitamins B<sub>6</sub>, B<sub>12</sub> and folic acid. Vitamin B<sub>2</sub> contributes to normal iron metabolism.
- EPA and DHA contribute to the normal **function of the heart** with a daily intake of at least 250 mg

### Applications and recommended use

Helps to maintain mental focus and healthy eyes, to manage mental stress and fatigue, and to increase natural resistance. Suitable for students, managers, drivers, athletes or the elderly.

### Typical indications for EPA+DHA with vitamin D<sub>3</sub>, B<sub>6</sub>, B<sub>12</sub>, biotin and folic acid:

- Supporting cognitive functions (attention, memory)
- ADHD-like symptoms (mainly attention problems)
- Mild Cognitive Impairment (MCI, a pre-dementia stage)
- Support in mild to moderate major depression

### Typical indications for EPA+DHA with lutein and zeaxanthin

- Dry eyes (age-related, lens wearers, computer users)
- Inhibiting the progression of age-related macular degeneration (AMD)
- Prevention of cataract

### Typical indications for the B vitamins (B<sub>2</sub>, B<sub>5</sub>, B<sub>12</sub>, folic acid) with vitamin D<sub>3</sub>, selenium and Siberian ginseng:

- Fatigue and stress
- Mild anaemia
- Increase in natural resistance (e.g. flu prevention)

## Interactions and precautions

No side effects are known when is used correctly.

## Scientific information

### Brain food

The omega-3 fatty acid **docosahexaenoic acid (DHA)** is a building block of the grey matter in the brain, and accumulates in brain regions taking part in learning and memory (e.g. brain cortex and hippocampus).<sup>1,2</sup> With the help of imaging techniques (magnetic resonance) researchers were able to ascertain that higher intakes of omega-3 fatty acids were associated with larger grey matter volumes in the prefrontal cortex, hippocampus and amygdala of healthy adults.<sup>3</sup> DHA provides a certain suppleness to the cell membranes of nerve cells, which in turn supports membrane proteins to function better, and neurotransmission to run more smoothly.

Moreover, DHA improves cerebral blood flow and is the precursor for neuroprotectins and resolvins that protect nerve tissue against inflammation and oxidative stress.

Brain tissue contains 250 to 300 times less of the omega-3 fatty acid **eicosapentaenoic acid (EPA)** than DHA, however EPA does also play a role. EPA likewise contributes to improved cerebral blood flow and is the precursor of powerful anti-inflammatory eicosanoids.<sup>1,2</sup> It usually takes 3 months for DHA to be fully incorporated into cell membranes (and to confer an optimal effect), while the effect of EPA is already noticeable after 4 weeks.<sup>4</sup> EPA seems of more importance than DHA to improve depressive feelings (formulas with more EPA than DHA gave significant improvements in major depression, while formulas with more DHA than EPA did not).<sup>5,6</sup>

Additionally, EPA seems also to be the most important omega-3 fatty acid to reduce attention problems in a subgroup of ADHD patients.<sup>7</sup> Omega-3 supplementation positively influences concentration and short-term-memory in both ADHD children and children with a normal development, especially in cases of omega-3 deficiency.<sup>8,9</sup> To improve memory in the elderly DHA has been studied most. Individuals with Mild Cognitive Impairment (MCI, probably a pre-dementia stage) who are not a carrier of the ApoE ε4-gene experience the best improvements upon DHA rich supplementation.<sup>1,10-12</sup>

**Vitamin D** also supports brain function. In research with the best study designs, vitamin D supplementation improved depressive symptoms.<sup>13</sup> Vitamin D activates the enzyme responsible for the conversion of tryptophan to serotonin (the neurotransmitter that influences memory, mood, self-confidence, appetite). In order to increase serotonin levels vitamin D cooperates well with EPA and DHA. EPA is expected to increase presynaptic serotonin release through inhibiting the synthesis of E2 series prostaglandins, while DHA improves postsynaptic serotonin receptor action by increasing cell membrane fluidity.<sup>14</sup>

**Vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, biotin** and **folic acid** play physiological roles in the maintenance of many psychological functions such as concentration, learning, memory and reasoning. For instance, these vitamins stimulate neurotransmitter synthesis.<sup>15,16</sup> Classical symptoms of a deficiency for vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, biotin and folic acid are confusion, memory loss, depression and concentration problems, respectively.<sup>16,17</sup> Data from the VITACOG trial (Homocysteine and B Vitamins in Cognitive Impairment) indicated that high dose B vitamin supplementation (20 mg vitamin B<sub>6</sub> + 0.5 mg vitamin B<sub>12</sub> + 800 µg folic acid per dag) slowed brain

wasting (atrophy) in patients with mild cognitive impairment by 40%, but only when their omega-3 blood levels were already high. In patients with low blood levels of omega-3 vitamin B supplementation had no beneficial effect. This new finding stresses an important synergy between B vitamins and omega-3 (EPA+DHA) against age-related brain wasting.<sup>18</sup>

## Eye health

The omega-3 fatty acid **DHA** is selectively incorporated and retained in the rod outer segments of the retina, where DHA supports regeneration of the light-sensitive rhodopsin pigment. Light absorption by rhodopsin is the first step in visual biochemistry. By maintaining rhodopsin in the active state DHA supports phototransduction, the process by which incoming light is converted into electrical signals that go straight to the visual centres in the brain. Through its conversion into neuroprotectin D1 (NPD1) DHA contributes to protecting retinal and corneal cells against oxidative stress and inflammation. The omega-3 fatty acid **EPA** also has a vital role in the eyes' blood circulation.<sup>19</sup> Participants in the NAT2 trial (Nutritional AMD Treatment 2 study) who achieved a high enough omega-3 index (mean omega-3 index of 8.68) were able to slow down development of age-related macular degeneration.<sup>20</sup> A meta-analysis of 7 trials comprising a total of 790 participants with dry eye syndrome indicated symptom improvements upon omega-3 supplementation (300 to 750 mg EPA+DHA per day): tear production and tear-film stability were improved.<sup>21</sup>

**Lutein and zeaxanthin** are highly concentrated in the lens and macula of the retina, where they act as blue light filters and antioxidants preventing the lens to go cloudy and supporting vision. Lutein is found in the non-central part of the macula and helps recovering from blinding light more efficiently (low-contrast vision). Zeaxanthin is located in the central zone of the macula (the fovea) and helps discriminating different forms (high-contrast vision). In the AREDS2 trial (Age-Related Eye Disease Study 2) with 4203 patients with age-related macular degeneration daily use of 10 mg lutein + 2 mg zeaxanthin induced a 10% risk reduction of progression to advanced macular degeneration.<sup>22</sup> In a meta-analysis of 6 observational studies comprising 41999 participants including 4416 cataract patients lutein and zeaxanthin intake was associated with a reduced risk of age-related nuclear cataract formation (clouded vision originating in the centre of the lens). Every 300 µg/d increment in dietary lutein and zeaxanthin intake was associated with a 3% reduction in the risk of nuclear cataract.<sup>23</sup>

## Supporting natural resistance and vitality

Vitamins and minerals function as co-factors of various enzymes with a role in numerous metabolic reactions. B vitamins have a physiological role in energy metabolism (i.e. the production of energy for the body)<sup>24</sup>, and the vitamins B<sub>6</sub>, B<sub>12</sub>, D, folic acid and selenium allow the immune system to work properly<sup>25</sup>. For example, there is evidence that vitamin D helps protect against the occurrence of upper respiratory tract infections caused by the influenza virus by suppressing the production of pro-inflammatory substances.<sup>26,27</sup> Vitamin B<sub>6</sub> is required as coenzyme in the metabolism of antibodies and cytokines, vitamin B<sub>12</sub> deficiency leads to suppressed NK cell activity, while shortages of folic acid or selenium inhibit proper functioning of T lymphocytes.<sup>24,28,29</sup> These characteristics only serve as examples, since vitamins and minerals have a broad impact on immune system functioning. Siberian ginseng (*Eleutherococcus senticosus*) is a well-known adaptogen. Adaptogens increase stress resistance.<sup>30</sup>

## References

1. Stonehouse W. Does consumption of LC omega-3 PUFA enhance cognitive performance in healthy school-aged children and throughout adulthood? Evidence from clinical trials. *Nutrients* 2014; 6(7):2730-58.
2. Kuratko CN, Barrett EC, Nelson EB, Salem N Jr. The relationship of docosahexaenoic acid (DHA) with learning and behavior in healthy children: a review. *Nutrients* 2013; 5(7):2777-810.
3. Conklin SM, Gianaros PJ, Brown SM, Yao JK, Hariri AR, Manuck SB, Muldoon MF. Long-chain omega-3 fatty acid intake is associated positively with corticolimbic gray matter volume in healthy adults. *Neurosci Lett* 2007; 421(3):209-12.
4. Bauer I, Crewther S, Pipingas A, Sellick L, Crewther D. Does omega-3 fatty acid supplementation enhance neural efficiency? A review of the literature. *Hum Psychopharmacol* 2014; 29(1):8-18.
5. Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. *J Clin Psychiatry* 2011; 72(12):1577-84.
6. Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, Drago F, Caraci F. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PLoS One* 2014; 9(5):e96905.
7. Puri BK, Martins JG. Which polyunsaturated fatty acids are active in children with attention-deficit hyperactivity disorder receiving PUFA supplementation? A fatty acid validated meta-regression analysis of randomized controlled trials. *Prostaglandins Leukot Essent Fatty Acids* 2014; 90(5):179-89.
8. Bos DJ, Oranje B, Veerhoek ES, Van Diepen RM, Weusten JM, Demmelmair H, Koletzko B, de Sain-van der Velden MG, Eilander A, Hoeksma M, Durston S. Reduced Symptoms of Inattention after Dietary Omega-3 Fatty Acid Supplementation in Boys with and without Attention Deficit/Hyperactivity Disorder. *Neuropsychopharmacology* 2015 Mar 19.
9. Cooper RE, Tye C, Kuntsi J, Vassos E, Asherson P. Omega-3 polyunsaturated fatty acid supplementation and cognition: A systematic review and meta-analysis. *J Psychopharmacol* 2015; 29(7):753-763.
10. Cederholm T, Salem N Jr, Palmblad J.  $\omega$ -3 fatty acids in the prevention of cognitive decline in humans. *Adv Nutr* 2013; 4(6):672-6.
11. Mazereeuw G, Lanctôt KL, Chau SA, Swardfager W, Herrmann N. Effects of  $\omega$ -3 fatty acids on cognitive performance: a meta-analysis. *Neurobiol Aging* 2012; 33(7):1482.e17-29.
12. Belkouch M, Hachem M, Elgot A, Lo Van A, Picq M, Guichardant M, Lagarde M, Bernoud-Hubac N. The pleiotropic effects of omega-3 docosahexaenoic acid on the hallmarks of Alzheimer's disease. *J Nutr Biochem* 2016; 38:1-11.
13. Spedding S. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. *Nutrients* 2014; 6(4):1501-18.
14. Patrick RP, Ames BN. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. *FASEB J* 2015; 29(6):2207-2222.
15. Stahl SM. Novel therapeutics for depression: L-methylfolate as a trimonoamine modulator and antidepressant-augmenting agent. *CNS Spectr* 2007; 12(10):739-44.
16. Institute of Medicine (IoM). Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. 1998.
17. Wynn M, Wynn A. The danger of B12 deficiency in the elderly. *Nutr Health* 1998; 12(4):215-26.
18. Jernerén F, Elshorbagy AK, Oulhaj A, Smith SM, Refsum H, Smith AD. Brain atrophy in cognitively impaired elderly: the importance of long-chain  $\omega$ -3 fatty acids and B vitamin status in a randomized controlled trial. *Am J Clin Nutr* 2015; 102(1):215-21.
19. SanGiovanni JP1, Chew EY. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina. *Prog Retin Eye Res* 2005; 24(1):87-138.
20. Souied EH, Delcourt C, Querques G, Bassols A, Merle B, Zourdani A, Smith T, Benlian P; Nutritional AMD Treatment 2 Study Group. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study. *Ophthalmology* 2013; 120(8):1619-31.
21. Liu A, Ji J. Omega-3 essential fatty acids therapy for dry eye syndrome: a meta-analysis of randomized controlled studies. *Med Sci Monit* 2014; 20:1583-9.
22. McCusker MM, Durrani K, Payette MJ, Suchecki J. An eye on nutrition: The role of vitamins, essential fatty acids, and antioxidants in age-related macular degeneration, dry eye syndrome, and cataract. *Clin Dermatol* 2016; 34(2):276-85.
23. Ma L, Hao ZX, Liu RR, Yu RB, Shi Q, Pan JP. A dose-response meta-analysis of dietary lutein and zeaxanthin intake in relation to risk of age-related cataract. *Graefes Arch Clin Exp Ophthalmol* 2014; 252(1):63-70.

24. Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. *Chem Biol Interact* 2006; 163(1-2):94-112.
25. Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. *Ann Nutr Metab* 2007;51(4):301-23.
26. Bergman P, Lindh AU, Björkhem-Bergman L, Lindh JD. Vitamin D and Respiratory Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLoS One*.2013; 8(6):e65835.
27. Greiller CL, Martineau AR. Modulation of the Immune Response to Respiratory Viruses by Vitamin D. *Nutrients* 2015;b7(6):4240-4270.
28. Courtemanche C, Elson-Schwab I, Mashiyama ST, Kerry N, Ames BN. Folate deficiency inhibits the proliferation of primary human CD8+ T lymphocytes in vitro. *J Immunol* 2004; 173(5):3186-92.
29. Rühl R. Effects of dietary retinoids and carotenoids on immune development. *Proc Nutr Soc* 2007; 66(3):458-69.
30. Monograph. *Eleutherococcus senticosus*. *Altern Med Rev* 2006; 11(2):151-5.