

HomocysteineBalance is a combination of 7 ingredients that contribute to homocysteine regulation.

Homocysteine is a sulfur amino acid that is important for cell metabolism. It is produced in the body as a residual substance of certain chemical reactions such as cell renovation, and it's involved in the development of cardiovascular and cerebrovascular diseases. It occurs as a result of the normal metabolism of methionine which is obtained through food intake. High homocysteine levels are associated with coronary heart disease ⁽¹⁾ and especially cerebrovascular accidents ⁽²⁾, neurological diseases ⁽³⁻⁴⁾ and reproductive problems ⁽⁵⁻⁸⁾.

Factors that increase blood homocysteine levels:

- Genetic factors.
- Dietary deficiency of folate, vitamins B6 or B12.
- Renal or hepatic insufficiency, hypothyroidism, neoplasia, etc.
- Medications and toxins (excessive consumption of coffee and/or alcohol, smoking, etc.).
- The consumption of animal products that increase cholesterol oxides (oxysterols) in the blood. Meat has a lot of methionine which is a precursor to homocysteine.

Homocysteine is considered high (hyperhomocysteinemia) at levels of over 10.4 µmol/L in women and 11.4 µmol/L in men.

Ingredients: Betaine, natural lemon/lime flavour, inositol, choline (bitartrate), acidity regulator (malic acid), zinc bisglycinate, anticaking agent: silicon dioxide, sweetener (steviol glycosides from *Stevia rebaudiana* and isomaltulose), methylcobalamin (vit. B12), calcium-L-methylfolate (folate), pyridoxal 5'-phosphate (vit. B6).

Nutricional information:	½ scoop (2,344 g)
Betaine	1 g
Inositol	0,375 g
Choline (bitartrate)	0,25 g
Zinc (from zinc bisglycinate)	7,5 mg (75%*)
Vitamin B6 (pyridoxine) (from 2,5 mg pyridoxal 5'phosphate)	1,7 mg (121%*)
Vitamin B12 (methylcobalamin)	375 µg (15.000 %*)
Folate (from calcium-L-methylfolate)	250 µg (125%*)

*NRV: Nutrient Reference Value in %.

Size and format:

285 g

Recommended daily dose:

½ scoop daily with food. Mix with 150-250 ml of water (dilute to taste).

Do not exceed the recommended daily dose.

Indications and uses:

- Hyperhomocysteinemia.
- Prevention of cardiovascular disease (ischemic cerebrovascular accident, atherosclerosis, etc.).
- Prevention of neurological diseases (cerebral atrophy, depression, etc.).
- Reproductive problems (polycystic ovary syndrome).

Cautions: Consult a health-care practitioner prior to use if you are pregnant or breast-feeding, or if you have a special medical condition (high cholesterol). A daily intake of over 4 g of betaine can considerably increase blood cholesterol levels.

BETAINE: homocysteine concentrations can be reduced through greater remethylation of homocysteine into methionine. Betaine (trimethylglycine) acts as a methyl group donor in this relationship. The administration of betaine supplements reduces plasma homocysteine concentrations ⁽⁹⁻¹⁰⁾. In the case of hypochlorhydria, an insufficiency of the gastric secretion of hydrochloric acid, supplementing with betaine HCl helps maintain optimal levels of hydrochloric acid, improving digestion and associated symptoms ⁽¹¹⁻¹²⁾.

FOLATE: 5-methyltetrahydrofolate (calcium L-methylfolate) is a substrate for the enzyme methionine synthase, which remethylates homocysteine in order to form methionine. Diverse studies indicate a strong association between the intake of dietary folate and plasma homocysteine concentrations ⁽¹³⁾. A 2007 meta-analysis found that the administration of folic acid supplements significantly reduced the risk of cerebrovascular accidents by 18% and had an even greater benefit, a risk reduction of almost 30 %, in studies where folic acid was administered for over 36 months ⁽¹⁴⁾. Another study in patients with a high risk for cardiovascular disease revealed that the administration of folic acid supplements for 18 months reduced carotid intima-media thickness, which is a risk measurement for atherosclerosis ⁽¹⁵⁾. **VITAMIN B12:** the remethylation of

homocysteine into methionine requires vitamin B12 as a cofactor for the enzyme methionine synthase. In a meta-analysis⁽¹⁶⁾, it was found that vitamin B12 is less effective for decreasing total homocysteine than folic acid. The effect of vitamin B12 is generally decreased by the greater role that folate plays in homocysteine determination. Once folate levels are optimized, a clear dependence appears between plasma homocysteine levels and supplementation with vitamin B12⁽¹⁷⁾.

VITAMIN B6 the metabolically active form of vitamin B6, pyridoxal 5'-phosphate, is an enzymatic cofactor of cystathionine β -synthase, which participates in the catabolism of homocysteine into cystathionine in the transsulfuration pathway. In diverse studies, the effect of the administration of vitamin B6 along with folate and vitamin B12 on plasma homocysteine levels has been seen⁽¹⁸⁻²²⁾. Low vitamin B6 levels are strongly related to an increased risk of cardiovascular disease⁽²³⁾. This finding backs studies on animals with vitamin B6 deficiency and epidemiological studies⁽²⁴⁾ in which an association has been seen between low vitamin B6 levels and vascular diseases, which could be explained by the relationship between inflammation and low levels of vitamin B6⁽²⁵⁾. It is known that a low intake of folate, vitamin B12 and vitamin B6 raises plasma homocysteine⁽²⁾, while their supplementation can reduce it. Vitamins B6 and B12 act as coenzymes in homocysteine metabolism. There are several studies showing that the administration of folate and/or a combination of folate, B12 and B6 not only reduces homocysteine, but also significantly reduces the risk of a cerebrovascular accident⁽²⁶⁻²⁷⁾.

INOSITOL: involved in cell membrane integrity, it transports fats from the liver and increases the action of insulin in patients with polycystic ovary syndrome, improving ovulation and decreasing serum androgen concentrations, blood pressure and plasma triglyceride concentrations. Inositol can also be involved in depression. People who are depressed can have lower inositol levels than normal in their spinal fluid. Inositol also participates in the action of serotonin, a neurotransmitter known for its important role in depression⁽²⁸⁻³¹⁾.

CHOLINE: is related to blood homocysteine concentrations. Homocysteine can catabolize to cysteine through the transsulfuration pathway or remethylate into methionine. Choline can be oxidized in the body in order to produce betaine (trimethylglycine, TMG) through the enzyme betaine-homocysteine methyltransferase (BHMT)⁽³²⁾. Choline is also essential for synthesizing the structural components of cell membranes, is involved in cell signaling, is a precursor to the neurotransmitter acetylcholine and helps eliminate fat and cholesterol from the liver⁽³³⁾. Choline deficiency is associated with high plasma homocysteine concentrations after methionine administration⁽³⁴⁾. One study examined the relationship between choline intake and homocysteine levels as measured by food frequency questionnaires and blood analyses. The highest intake of choline and betaine was related to the lowest levels of homocysteine, regardless of other determining factors, such as folate and other B vitamins⁽³⁵⁾. Several studies show the effectiveness of choline at reducing homocysteine levels⁽³⁵⁻³⁶⁾.

ZINC: the enzymes betaine-homocysteine methyltransferase and methionine synthase are metalloenzymes of zinc. Zinc is also needed for the conversion of homocysteine into cysteine and glutathione. In a randomized, double-blind, controlled, crossover study, 50 patients with type II diabetes and microalbuminuria were subdivided into two groups and were supplemented with 30 mg per day of zinc (group 1) or placebo (group 2) for three months with a washout period of four weeks. The researchers concluded that zinc supplementation reduced serum homocysteine and increased concentrations of vitamin B12 and folate in type II diabetic patients with microalbuminuria⁽³⁷⁾. Other studies confirm that zinc supplementation reduces plasma homocysteine levels⁽³⁸⁾.

References:

- 1) Wald, David S., Malcolm Law, and Joan K. Morris. "Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis." *Bmj* 325.7374 (2002): 1202.
- 2) Hoque, M. M., M. Z. Rahman, and M. R. Rahman. "Role of homocysteine in cerebrovascular disease." *Mymensingh medical journal: MMJ* 17.2 Suppl (2008): S39-42.
- 3) Miwa, Kaori, et al. "Increased total homocysteine levels predict the risk of incident dementia independent of cerebral small-vessel diseases and vascular risk factors." *Journal of Alzheimer's Disease* 49.2 (2016): 503-513.
- 4) Bryce, B., et al. "Homocysteine and Cerebral Atrophy." *Journal of Alzheimer's Disease* 62.2 (2018): 877-885.
- 5) Maharjan, Pranita, and Peng Dan Hong. "The Effects of Plasma Homocysteine in PCOS Women: A Review." *Open Journal of Obstetrics and Gynecology* 8.01 (2018): 39.
- 6) Forges, Thierry, et al. "Impact of folate and homocysteine metabolism on human reproductive health." *Human reproduction update* 13.3 (2007): 225-238.
- 7) Del, A. Bianco, et al. "Recurrent spontaneous miscarriages and hyperhomocysteinemia." *Minerva ginecologica* 56.5 (2004): 379-383.
- 8) Chakraborty, Pratip, et al. "Recurrent pregnancy loss in polycystic ovary syndrome: role of hyperhomocysteinemia and insulin resistance." *PLoS One* 8.5 (2013): e64446.
- 9) Olthof, Margreet R., et al. "Low dose betaine supplementation leads to immediate and long term lowering of plasma homocysteine in healthy men and women." *The Journal of nutrition* 133.12 (2003): 4135-4138.

- 10) McRae, Marc P. "Betaine supplementation decreases plasma homocysteine in healthy adult participants: a meta-analysis." *Journal of chiropractic medicine* 12.1 (2013): 20-25.
- 11) Yago, Marc R., et al. "Gastric reacidification with betaine HCl in healthy volunteers with rabeprazole-induced hypochlorhydria." *Molecular pharmaceutics* 10.11 (2013): 4032-4037.
- 12) Day, Christopher R., and Stephen A. Kempson. "Betaine chemistry, roles, and potential use in liver disease." *Biochimica et Biophysica Acta (BBA)-General Subjects* 1860.6 (2016): 1098-1106.
- 13) Nygard, Ottar, et al. "Major lifestyle determinants of plasma total homocysteine distribution: the Hordaland Homocysteine Study." *The American journal of clinical nutrition* 67.2 (1998): 263-270.
- 14) Wang, Xiaobin, et al. "Efficacy of folic acid supplementation in stroke prevention: a meta-analysis." *The Lancet* 369.9576 (2007): 1876-1882.
- 15) Ntaios, George, et al. "The effect of folic acid supplementation on carotid intima-media thickness in patients with cardiovascular risk: a randomized, placebo-controlled trial." *International journal of cardiology* 143.1 (2010): 16-19.
- 16) Homocysteine Lowering Trialists' Collaboration. "Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials." *Bmj* 316.7135 (1998): 894-898.
- 17) Quinlivan, E. P., et al. "Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease." *The Lancet* 359.9302 (2002): 227-228.
- 18) Vermeulen, EGJE GJ, et al. "Effect of homocysteine-lowering treatment with folic acid plus vitamin B6 on progression of subclinical atherosclerosis: a randomised, placebo-controlled trial." *The Lancet* 355.9203 (2000): 517-522.
- 19) Smith, A. David, et al. "Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial." *PloS one* 5.9 (2010): e12244.
- 20) Almeida, Osvaldo P., et al. "B-vitamins reduce the long-term risk of depression after stroke: the VITATOPS-DEP trial." *Annals of neurology* 68.4 (2010): 503-510.
- 21) Till, Uwe, et al. "Decrease of carotid intima-media thickness in patients at risk to cerebral ischemia after supplementation with folic acid, vitamins B6 and B12." *Atherosclerosis* 181.1 (2005): 131-135.
- 22) McKinley, Michelle C., et al. "Low-dose vitamin B-6 effectively lowers fasting plasma homocysteine in healthy elderly persons who are folate and riboflavin replete." *The American journal of clinical nutrition* 73.4 (2001): 759-764.
- 23) Kelly, Peter J., et al. "Low vitamin B6 but not homocyst (e) ine is associated with increased risk of stroke and transient ischemic attack in the era of folic acid grain fortification." *Stroke* 34.6 (2003): e51-e54.
- 24) Rimm, Eric B., et al. "Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women." *Jama* 279.5 (1998): 359-364.
- 25) Kelly, P. J., et al. "Inflammation, homocysteine, and vitamin B6 status after ischemic stroke." *Stroke* 35.1 (2004): 12-15.
- 26) Saposnik, Gustavo, et al. "Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from the HOPE 2 trial." *Stroke* 40.4 (2009): 1365-1372.
- 27) Wang, Xiaobin, et al. "Efficacy of folic acid supplementation in stroke prevention: a meta-analysis." *The Lancet* 369.9576 (2007): 1876-1882.
- 28) Colodny, Lisa, and R. L. Hoffman. "Inositol-clinical applications for exogenous use." *Alternative Medicine Review* 3 (1998): 432-447.
- 29) Unfer, V., et al. "Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials." *Gynecological Endocrinology* 28.7 (2012): 509-515.
- 30) Benelli, Elena, et al. "A combined therapy with myo-inositol and D-chiro-inositol improves endocrine parameters and insulin resistance in PCOS young overweight women." *International journal of endocrinology* 2016 (2016).
- 31) Mukai, Tomohiko, et al. "A meta-analysis of inositol for depression and anxiety disorders." *Human Psychopharmacology: Clinical and Experimental* 29.1 (2014): 55-63.
- 32) Finkelstein, J. D. "The metabolism of homocysteine: pathways and regulation." *European journal of pediatrics* 157.2 (1998): S40-S44.
- 33) Zeisel, SH. "Choline, homocysteine, and pregnancy." *The American Journal of Clinical Nutrition* 82.4 (2005): 719-720.
- 34) da Costa, Kerry-Ann, et al. "Choline deficiency in mice and humans is associated with increased plasma homocysteine concentration after a methionine load-." *The American journal of clinical nutrition* 81.2 (2005): 440-444.
- 35) Olthof, Margreet R., et al. "Choline supplemented as phosphatidylcholine decreases fasting and postmethionine-loading plasma homocysteine concentrations in healthy men-." *The American journal of clinical nutrition* 82.1 (2005): 111-117.
- 36) Wallace, Julie MW, et al. "Choline supplementation and measures of choline and betaine status: a randomised, controlled trial in postmenopausal women." *British Journal of Nutrition* 108.7 (2012): 1264-1271.
- 37) Heidarian, Esfandiar, et al. "Effect of zinc supplementation on serum homocysteine in type 2 diabetic patients with microalbuminuria." *The review of diabetic studies: RDS* 6.1 (2009): 64.
- 38) Pakfetrat, Maryam, et al. "Effects of zinc supplement on plasma homocysteine level in end-stage renal disease patients: a double-blind randomized clinical trial." *Biological trace element research* 153.1-3 (2013): 11-15.