# Methyl SAP

*Science-based B vitamins and betaine for homocysteine control*

A high level of homocysteine in circulation is an independent risk factor for the development of disability and death from cardiovascular disease (CVD), including stroke. CVD risk increases proportionately by 6% to 7% with every 1 µmol/L increase in blood homocysteine. Elevated blood homocysteine is also thought to relate to onset of diseases of the brain and kidneys, and to diabetic complications. Elevated homocysteine levels are often observed in the elderly and in individuals with compromised nutrition, gastrointestinal disorders, or a genetic tendency for hyperhomocysteinemia. **Methyl SAP** provides a combination of scientifically supported doses of B vitamins (folate, vitamin $B_6$, vitamin $B_{12}$) and betaine to optimize breakdown of homocysteine, thus preventing its buildup in the blood.

## ACTIVE INGREDIENTS

**Each vegetable capsule contains:**

| | |
|---|---|
| L-Methylfolate (calcium L-5-methyltetrahydrofolate) | 400 mcg |
| Vitamin $B_{12}$ (methylcobalamin) | 500 mcg |
| Vitamin $B_6$ (pyridoxal-5′-phosphate) | 20 mg |
| Betaine (trimethylglycine) | 668 mg |

**Other ingredients:** Microcrystalline cellulose, vegetable magnesium stearate, and silicon dioxide in a vegetable capsule composed of vegetable carbohydrate gum and purified water.

**This product is non-GMO.**

**Contains no:** Gluten, soy, wheat, corn, eggs, dairy, yeast, citrus, preservatives, artificial flavour or colour, starch, or sugar.

**Methyl SAP** (B vitamins and betaine) contains 60 capsules per bottle.

## DIRECTIONS FOR USE

**Adults: Take 2 capsules daily** or as directed by your healthcare practitioner. Consult a healthcare practitioner for use beyond 12 weeks.

2 capsules provide 800 mcg of L-methylfolate, 1 mg of vitamin $B_{12}$, 40 mg of vitamin $B_6$, and 1336 mg of betaine.

## INDICATIONS

**Methyl SAP** can help:

- Lower blood homocysteine levels.
- Support the body's B vitamin–dependent pathways.

## FORM AND DOSE TO GUARANTEE EFFICACY AND SAFETY

- The L-methylfolate, methylcobalamin, pyridoxal-5′-phosphate, and trimethylglycine forms used in this blend are better absorbed and more bioavailable than other forms of the same compounds.
- By following Canadian and US Daily Recommended Intake (DRI), Recommended Daily Allowances (RDA) and Upper Limits (UL) as well as cutting-edge scientific evidence, the doses of L-methylfolate, vitamin $B_{12}$, vitamin $B_6$, and betaine in **Methyl SAP** have been carefully selected to ensure efficacy and safety.

## PURITY AND CLEANLINESS

All ingredients listed for each **Methyl SAP** lot number have been tested by an ISO 17025–accredited third-party laboratory for identity, potency, and purity.


Scientific Advisory Panel (SAP): adding nutraceutical research to achieve optimum health

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## WHAT IS HOMOCYSTEINE?

Total homocysteine is a non-protein forming, highly reactive sulfur amino acid. It is an intermediary product of methionine metabolism and can be remethylated to methionine (a methyl donor in nucleic acid metabolism) or metabolized to cysteine (a precursor of glutathione) through biochemical pathways dependent on the presence of folic acid (folate), vitamin B12, vitamin B6 and betaine (see Fig. 1).[1]

Blood homocysteine can be measured in a fasted or postmethionine load state. In a fasted state, blood homocysteine above approximately 10 µmol/L is considered elevated and a potential risk factor for certain diseases, most notably cardiovascular disease (CVD).[2]

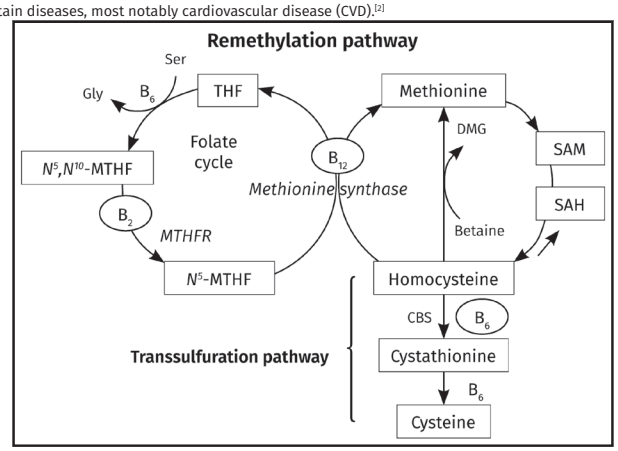


**Figure 1. Homocysteine Metabolism: Biochemical Pathways[3]**

Ser = serine; Gly = glycine; MTHF = methylenetetrahydrofolate; MTHFR = $N^5$,$N^{10}$-methylenetetrahydrofolate reductase; THF = tetrahydrofolate; SAM = *S*-adenosylmethionine; SAH = *S*-adenosylhomocysteine; DMG = dimethylglycine; CBS = cystathionine β-synthase.

## WHO HAS HOMOCYSTEINE IMBALANCE?

Elevation of intracellular and subsequently plasma homocysteine levels occurs when the remethylation route or saturation of the transsulfuration pathway (see Fig. 1) is inhibited as a result of an inadequate presence of substrate, cofactor or enzyme.[2] Such increases are observed with advancing age, in vascular disease patients, in individuals homozygous for a genetic mutation in the gene encoding MTHFR or CBS enzymes (see Fig. 1), and in younger men over younger women.[4] Levels can be influenced by the use of some medications, by lifestyle, and by clinical factors.[1]

Epidemiological research demonstrates B-vitamin intake inversely relates to total plasma homocysteine levels, and B-vitamin deficiency is the cause of over 60% of hyperhomocysteinemia cases.[2, 4]

Those at greater risk for clinically significant B-vitamin deficiency are vegetarians, the elderly, pregnant women, renal disease patients, and individuals with absorption disorders (i.e. irritable bowel syndrome) or malignant disease.[4]

## NUTRITION THERAPY IN HOMOCYSTEINE CONTROL

Folate, vitamin B12, vitamin B6 and betaine have been researched in clinical trials individually and in combination, and result in significantly lower blood homocysteine levels. The greatest response to treatment with B vitamins and folate is expected to occur in individuals with high baseline homocysteine and/or low baseline folate status.[4]

**Folate** — Dietary folic acid, like vitamin B6 and vitamin B12, is a water-soluble B-vitamin. It is obtained from green leafy vegetables and grains and is used in some grain products in North America as fortification. As a coenzyme in methionine metabolism (see Fig. 1), folic acid has a profound effect on homocysteine levels in humans.

The results of over 14 controlled human trials support supplementing 0.2 to 5 mg/d folate to lower blood homocysteine by 16 to 39%.[5, 6] In a recent trial, a dosage of 0.8 mg/d folate demonstrated maximal homocysteine lowering in CVD patients.[5]

**Vitamin B12 —** Vitamin B12 is a coenzyme in the formation of methionine (see Fig. 1). In the diet, B12 is obtained from fortified cereals, meat, fish, and poultry. With respect to optimizing homocysteine levels, based on human trials, an additional 7% lowering in blood homocysteine can be expected when 0.5 mg/d B12 is supplemented along with folate.[4, 5, 6]

**Vitamin B6 —** Vitamin B6, a coenzyme in the metabolism of methionine, can be found in the diet in fortified cereals, organ meats and fortified soy-based meat substitutes. Supplementing B6 (50–250 mg/d) has not been shown to consistently influence homocysteine levels in clinical trials;[6] however, this may be due to its effects being masked by those of folate and B12.[5]

Further, because B6 is an important cofactor in transsulfuration (see Fig. 1), it is recommended for supplementation along with folate and B12 for the optimization of homocysteine levels.[4, 5]

**Betaine** — Betaine is formed from the oxidation of choline, is found naturally in most living organisms, including humans, and is available in the diet from spinach, beets and broccoli. An alternative methyl donor in the remethylation of methionine (see Fig. 1), betaine, alone or combined with folic acid, at doses of 1.5 to 6 g has been demonstrated in clinical research to significantly lower blood homocysteine levels up to 20% both in subjects with severe hyperhomocysteinemia attributable to inborn errors in homocysteine metabolism, a group most commonly selected for betaine supplementation, but also in healthy men and women with blood homocysteine of about 12.5 to 25 µmol/L.[8]

## SAFETY OF B VITAMIN AND BETAINE SUPPLEMENTATION

Canadian and US federal standards have set recommended dietary allowances (RDA) and tolerable upper limits (UL) for effective and safe lifelong consumption of these vitamins (see Fig. 2).

**Figure 2. B-Vitamin Dietary Reference Intakes (Men, Women)[7]**

| | RDA | UL |
|---|---|---|
| **Folate (Adults 19 to >70 years)** | 400 mcg/d | 1000 mcg/d |
| **$B_6$ (Adults 19 to 50 years)** | 1.3 mg/d | 100 mg/d |
| **$B_{12}$ (Adults 14 to >70 years)** | 2.4 mcg/d | Not determined |

Note: Folate levels expressed above as dietary folate equivalents (DFE). 1 DFE = 1 µg of food folate = 0.6 µg of folic acid from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach. RDA = Recommended Daily Allowance; UL = Tolerable Upper Limit

## HOMOCYSTEINE, DISEASE AND NUTRITION RESEARCH

**Cardiovascular Disease** — Epidemiological research has consistently found an independent relationship between hyperhomocysteinemia (fasted or after an oral methionine load) and CVD or all-cause mortality.[4] Elevated homocysteine is thought to be responsible for 10% of total CVD risk.[2, 4] Further, research examining an elderly population concluded that each 1 µmol/L increase in plasma homocysteine concentration above 10 µmol/L is associated with a 6–7% increase in CVD risk, and it is suggested that reducing elevated plasma homocysteine levels may prevent up to 25% of all cardiovascular events in high-risk groups.[4]

Some opposition to this evidence includes less convincing prospective research and conflicting results as to the impact of homocysteine on lowering the risk of chronic disease events.[2, 9, 10] Mechanisms by which hyperhomocysteinemia increases risk of CVD are thought to be through increasing LDL-cholesterol oxidation,[3] vascular smooth muscle cell proliferation,[3] platelet and coagulation factor activation,[3] endothelial dysfunction,[3] age-related immune dysfunction,[5] induction of inflammation and inflammatory functions of endothelial cells,[5] and impairment of cardiac oxygen (O2) consumption regulation through increasing superoxide (O2–) formation and inhibition of nitric oxide (NO) action.[11]

**Neurological Disorders** — Studies, particularly in the elderly, observe that serum total homocysteine levels are negatively correlated with neuropsychological test scores, but the evidence is conflicting regarding a correlation between serum B-vitamin status and B-vitamin supplementation and cognitive impairment.[12] Despite these results, B12 supplemented with folate is recommended to support folate utilization and for prevention of neurodegenerative damage including Alzheimer's disease.[4, 6]

**Diabetes** — Plasma homocysteine levels are elevated in patients with diabetes, particularly type 2 diabetes, as well as in individuals who exhibit insulin resistance.[13] In addition, medications (i.e. metformin and glitazones) and therapy with insulin can raise or lower homocysteine levels.[13] Some research has shown that deterioration of renal function is a precursor to elevated homocysteine in patients with diabetes. Homocysteine does not appear to be linked to a diabetic's level of glycemic control.[13]

**Fertility** — Oxidative stress is a major contributor to an underperforming reproductive system. Oxidative stress and the resulting DNA methylation occur via a disrupted glutathione metabolic pathway, which is responsible for glutathione synthesis and homocysteine regulation.[14] Supplementation with 5-methyltetrahydrofolate has been proposed to reduce homocysteine levels in patients under consultation for infertility having methyltetrahydrofolate reductase (MTHFR) C677T single nucleotide polymorphism.[15] Similar studies have linked elevated homocysteine levels with oocyte maturity and poor embryo quality. Specifically, MTHFR gene variants have been associated with low response to follicle stimulation, reduced chances of live birth following in vitro fertilization, and low ovarian reserves.[16] Gene variants in this one carbon metabolic pathway also affect spermatogenesis, quality of sperm and overall male reproductive health.[17]

**Autism** — It has been postulated that magnesium deficiency may contribute to reduced methylation of homocysteine which leads to decreased genome transcriptome and low synaptic plasticity in autistic children. A study analyzing blood and hair magnesium levels and blood homocysteine levels found elevated homocysteine levels accompanied with low magnesium levels in hair of children diagnosed with autism.[18] Other studies have previously identified oxidative stress and impaired methylation in children suffering from autism.[19] Clinical trials are now being conducted with methyl B12 supplementation, which has been linked with improved methylation and methionine metabolism.[20]

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