

## Vitamin B9 | 5-methyltetrahydrofolate | folate | folic acid

### Summary of benefits

Supports the nervous system and reduces the risk of neural tube defects in newborns (49-51,106,107).

Improves brain function (51-53).

Helps protect against mental impairment and Alzheimer's disease (50-52).

### Foods rich in folate

- Dark green leafy vegetables (turnip greens, spinach, romaine lettuce, asparagus, Brussels sprouts, broccoli)
  - Beans
  - Peanuts
  - Sunflower seeds
  - Fresh fruits
  - Whole grains
  - Liver
  - Aquatic foods
  - Eggs
  - Fortified foods
- (136).

Folate, also known as vitamin B9, is an essential vitamin which comes in multiple forms. 5-methyltetrahydrofolate is the natural form and folic acid is the synthetic form. It's found naturally in low levels in most plant-based foods and some countries fortify their wheat grain with folate. Folate plays critical roles in supporting the growth of neonates and is involved in the methylation process ubiquitously throughout the body.

Folate is commonly known as the "pregnancy supplement" as women who are planning to conceive are advised to take a daily dose of 400 µg of folate. This is crucial in preventing neural tube defects (NTDs) that can occur when there is insufficient folate provided to the developing fetus during the formation of the neural tube. Folate supplements can help to prevent neural tube defects, including spina bifida and anencephaly, and getting enough folate during pregnancy reduces the likelihood that a child will be born with one of these conditions (106,107). The combination of food fortification and supplementation has significantly reduced the occurrence of NTDs.

In addition to its role in pregnancy, folate supports methylation processes. 5-methyltetrahydrofolate (5-MTHF or L-methylfolate), indirectly contributes to the production of S-Adenosyl Methionine (SAME) endogenously. This parallels the effects of supplements involved in the alternate pathway that support SAME levels, such as creatine and trimethylglycine (TMG). These supplements, including folate, have shown similarities in their potential to support serotonin-based medication (typically SSRIs) as an adjuvant, while typically benefiting women more than men, particularly in the context of depression.

Low blood folate levels are linked to poor mental function and an increased risk of dementia. Even folate levels that are technically normal but on the lower end of the spectrum might increase the risk of mental impairment in older adults.

Adequate folate intake may help protect against Alzheimer's disease (108,109).

In a 2019 study involving 180 adults with mild cognitive impairment, taking 400 mcg of folate daily for 2 years improved measures of brain function and reduced blood levels of proteins that are involved in Alzheimer's disease (110).

Folate supplements come in three common forms: folate, folic acid, and L-methylfolate. Folic acid is the most commonly used form but may have negative effects when overconsumed. L-methylfolate shows promise, especially for individuals with genetic mutations in the enzyme methylenetetrahydrofolate reductase which is responsible for converting 5,10-methylenetetrahydrofolate into the active form 5-methyltetrahydrofolate (5-MTHF). Supplementing with 5-methyltetrahydrofolate may bypass this genetically disadvantageous rate-limiting step. Moreover, L-methylfolate appears to be a promising agent for supporting S-Adenosyl methionine (S-AdoMet) levels, as S-AdoMet supplements can be expensive, and this pathway seems to handle a larger workload compared to the pathway involving creatine and TMG (49-53).

Using 5-MTHF instead of folic acid reduces the risk of masking haematological symptoms of vitamin B12 deficiency, reduces interactions with drugs that inhibit dihydrofolate reductase, and overcomes metabolic defects caused by methylenetetrahydrofolate reductase polymorphism (137). This being important, since for folic acid to be utilized by the body it must first be converted into tetrahydrofolate by dihydrofolate reductase (DHFR) (139).

Bioavailability studies have provided strong evidence that 5-methyltetrahydrofolate is at least as effective as folic acid in improving folate status, as measured by blood concentrations of folate and by functional indicators of folate status, such as plasma homocysteine levels (138). Folate (as 5-methyltetrahydrofolate or folic acid) promotes the conversion of homocysteine into methionine. High levels of homocysteine increases the risk of damage to blood vessel walls and blood clots, hence rendering one more susceptible to heart disease, myocardial infarction, or stroke.

## Dosage Rationale

Unlike other B-vitamins, folate may pose potential adverse side effects when taken in high doses. Prolonged exposure to levels up to 250% of the recommended daily allowance (RDA) may be associated with a relative increase in the rates of cancer, particularly colon cancer among the elderly. This has been demonstrated by acute increases in colon cancer rates when both Canada and the US introduced fortification, although rates have declined overall. Folate is a B-vitamin where balance should be maintained in everyday life, and high doses of supplemental folate should be avoided if not intended for specific purposes. It's for these reasons, the fact that 5-methyltetrahydrofolate is the superior and active form, and the RDA of folate is 400mcg, that we opted for just that amount of 5-methyltetrahydrofolate in our Super U formula. It's important to note that while these statements are based on available information in the scientific literature, it is always advisable to consult with a healthcare professional before making any changes to your supplementation or health routine.

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