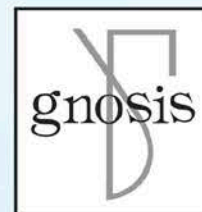




EXTRA[®] *folate-S*



advanced biotech

Extrafolate-S[®]

(6S)-5-Methyltetrahydrofolate Calcium Salt



Cellular Health



Prenatal & Lactation



Mood

Folate and the misleading concept

The terms *folic acid* and *folate* are often erroneously used interchangeably for the water-soluble B-complex vitamin.

FOLIC ACID



- Synthetic oxidized form of folate
- First synthesized in 1945
- More stable than natural form of folate
- No biological activity as is
- Needs to be metabolized
- Added in supplements and fortified foods
- Tolerable Upper Intake Level of 1 mg/day

FOLATES

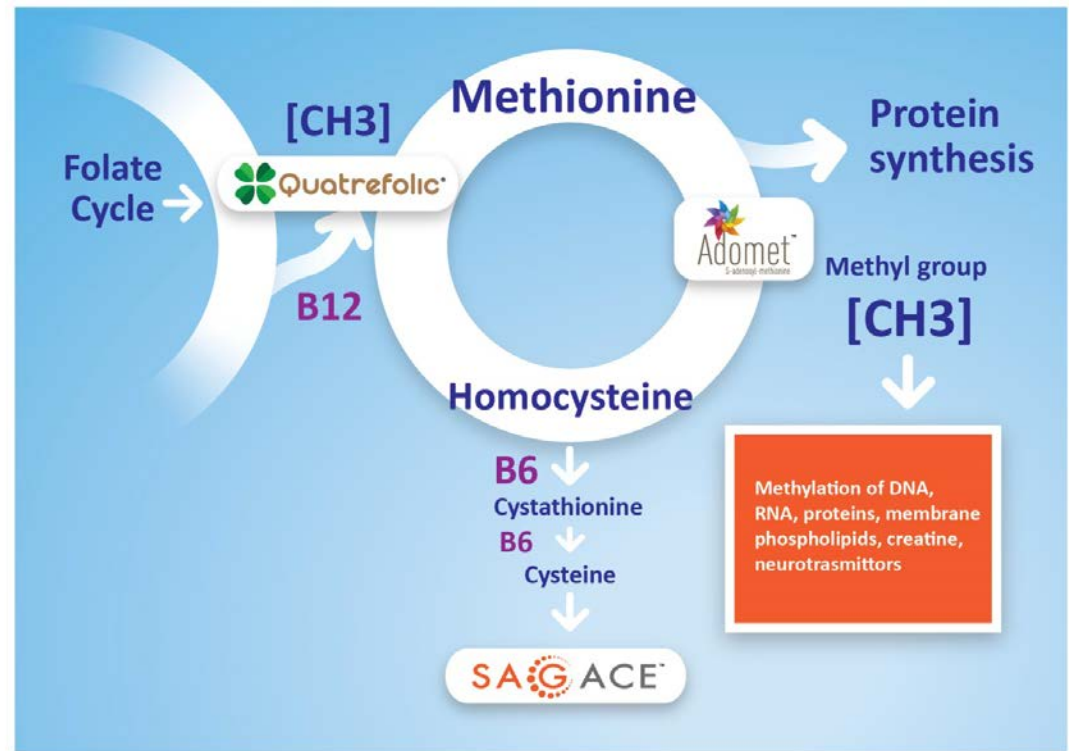


- Structurally-related compounds (as polyglutamated form)
- Naturally found in foods
- Must be hydrolyzed
- Biological activity similar to folic acid
- Unstable (food processing, manufacturing and storage)

(6S)-5-MTHF is a powerful player in One-Carbon Metabolism

Irrespective of whether ingested food contains natural or synthetically-derived folates, all are metabolized to 5-MTHF on uptake.

5-MTHF is one of the key components of the methylation cycle (one-carbon metabolism).



Extrafolate-S[®] features



- Biologically active in the pure form
- Essential form of folates stored and transported in the body
- The form crossing the blood-brain barrier
- Pure (6S) diastereoisomer > 99.0 %
- GRAS Status
- NDI (new Dietary Ingredient) Notification
- Strong intellectual property

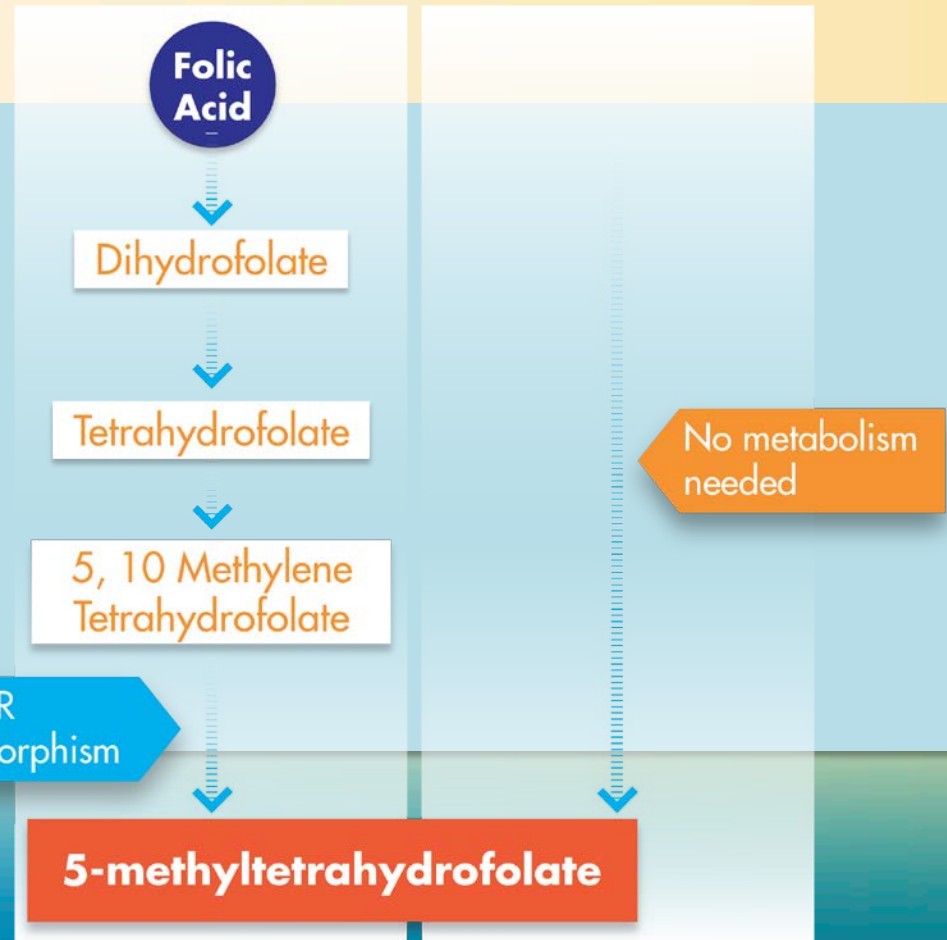


- No metabolism needed
- No UMFA (Unmetabolized Folic Acid) in the plasma
- No concerns associated to the MTHFR polymorphism
- No vitamin B12 deficiency masking effect

Extrafolate-S® is immediately bioavailable

Folic acid is metabolized in the mucosal cell before it can serve as a coenzyme for one-carbon transfer reaction while Extrafolate-S doesn't need.

Conversion steps in our body



10% of the world's population is affected by methylenetetrahydrofolate reductase (MTHFR) gene mutations.

In some ethnic groups polymorphism arrives to affect up to 20% of population.

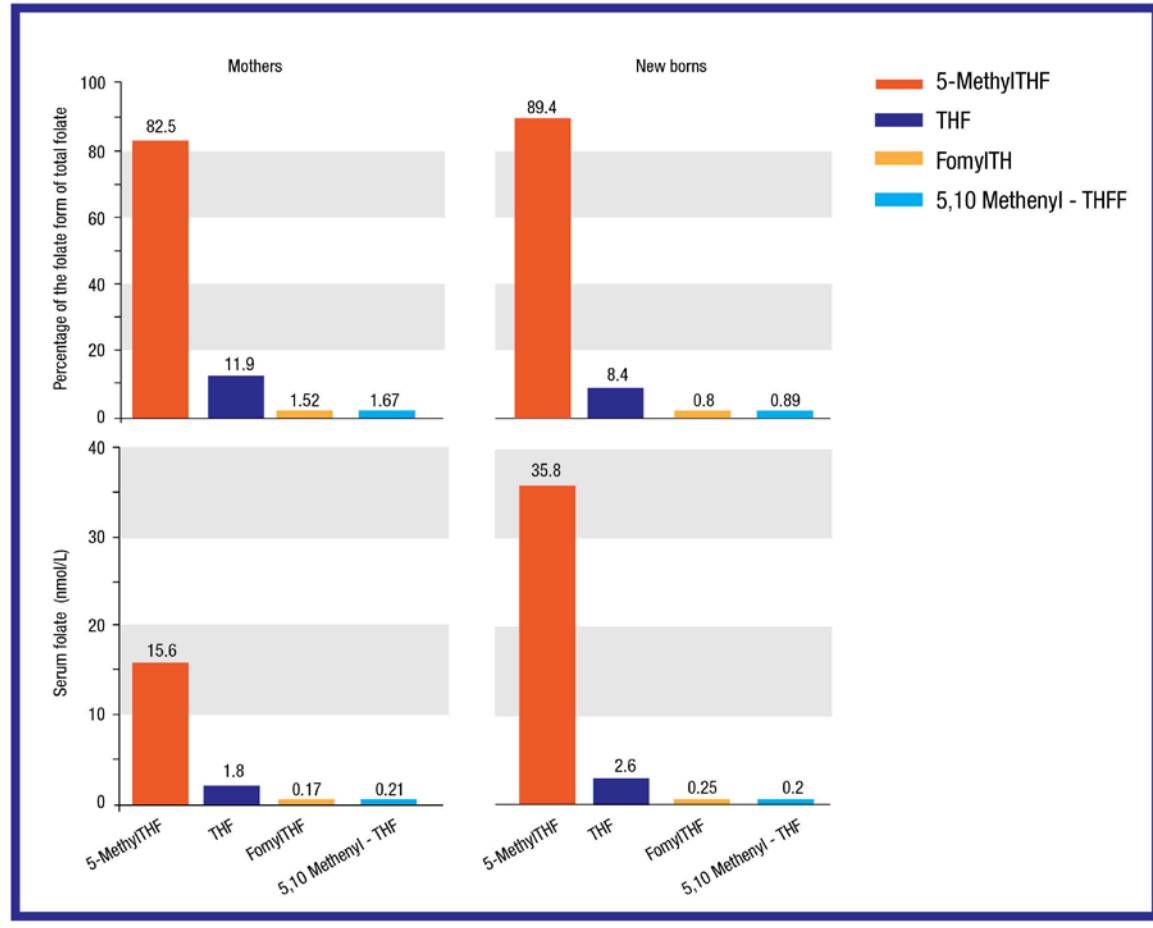
(6S)-5-Methyltetrahydrofolate is the only biological form of folate

95–98% of folate in serum or red blood cells is (6S)-5-MTHF.

(6S)-5-MTHF is the main folate form in cord blood (mean 89.4% of total folate).

The concentration of 5-MTHF in cord serum is approximately 2 times higher than in maternal serum.

Concentrations of the main folate forms and their percentage of total folate in maternal serum and umbilical cord serum from neonates



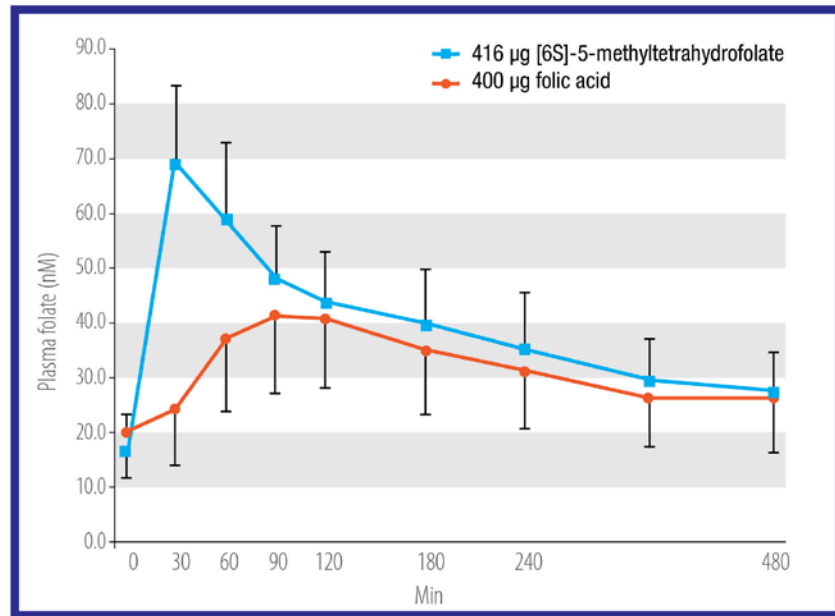
(6S)-5-Methyltetrahydrofolate is the most bioavailable form

In 2009 Prinz-Langenhorf et al. compared pharmacokinetic parameters of (6S)-5-MTHF and folic acid in women with or without MTHFR polymorphism (677C→T).

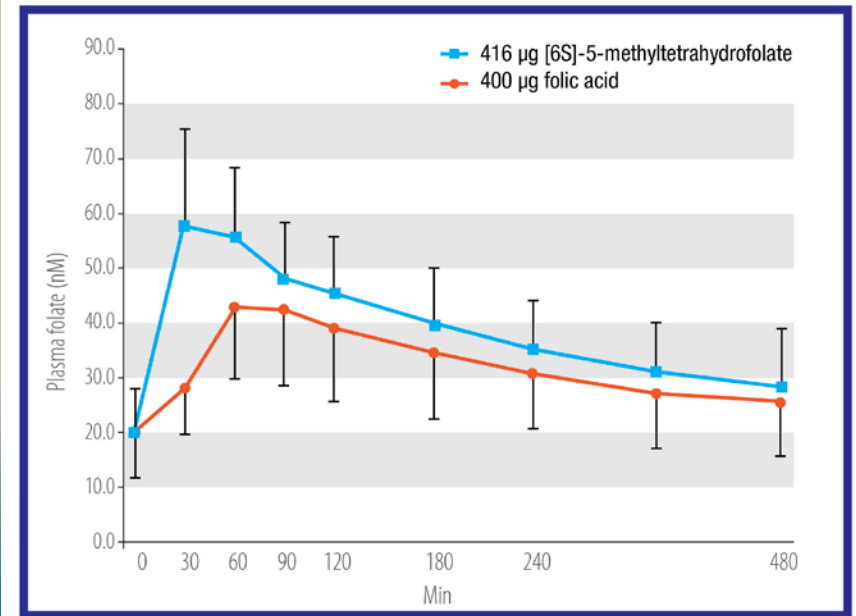
R E S U L T S

Physiological low dosage of (6S)-5-MTHF (416 µg) increases plasma folate more effectively than equimolar dosage of FA (400 µg), irrespective of the MTHFR polymorphism. The AUC concentration after (6S)-5-MTHF was twice as high as the AUC after administration of FA.

Total Plasma folate concentrations in TT genotype (MTHFR polymorphism)



Total Plasma folate concentrations in CC genotype (wild-type)



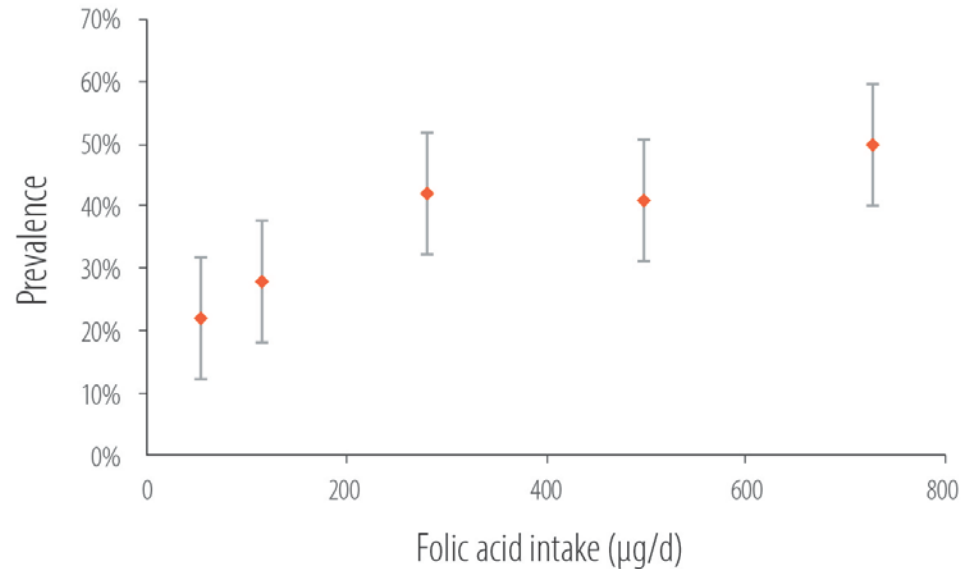
Extrafolate-S[®] doesn't expose the body to UMFA

Unmetabolized Folic Acid (UMFA) may be found in the circulation at doses of supplementation of **FA > 200µg**.

Recent scientific evidences suggest that UMFA may have potential adverse effect.

UMFA is associated with a reduction of immune system capacity to kill off malignant or pre-malignant cells.

Prevalence of detectable circulating unmetabolized folic acid by quintile category of estimated folic acid intake.



Extrafolate-S[®] doesn't mask vitamin B12 deficiency

High doses of FA can correct hematological signs of vitamin B12 deficiency often undiagnosed.

If vitamin B12 is deficient, the folate present in cells becomes "metabolically trapped" with:

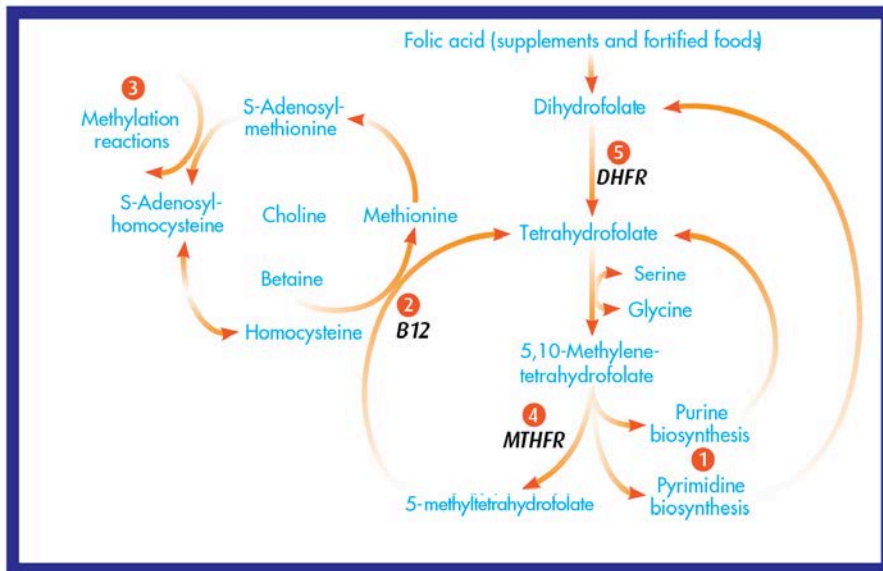
Impairment of purine and pyrimidine biosynthesis (pathway 1)

→ megaloblastic anemia

Methylation cycle block (pathway 2)

→ neurological damage progress

Principal Components of the Folate Biochemical Cycle.



R E S U L T S:

FA supplementantion may activate pathway 1 while Vit B12 deficiency remains unchecked, increasing risk of developing neurological complications

Extrafolate-S[®] is obtained through a green purification process

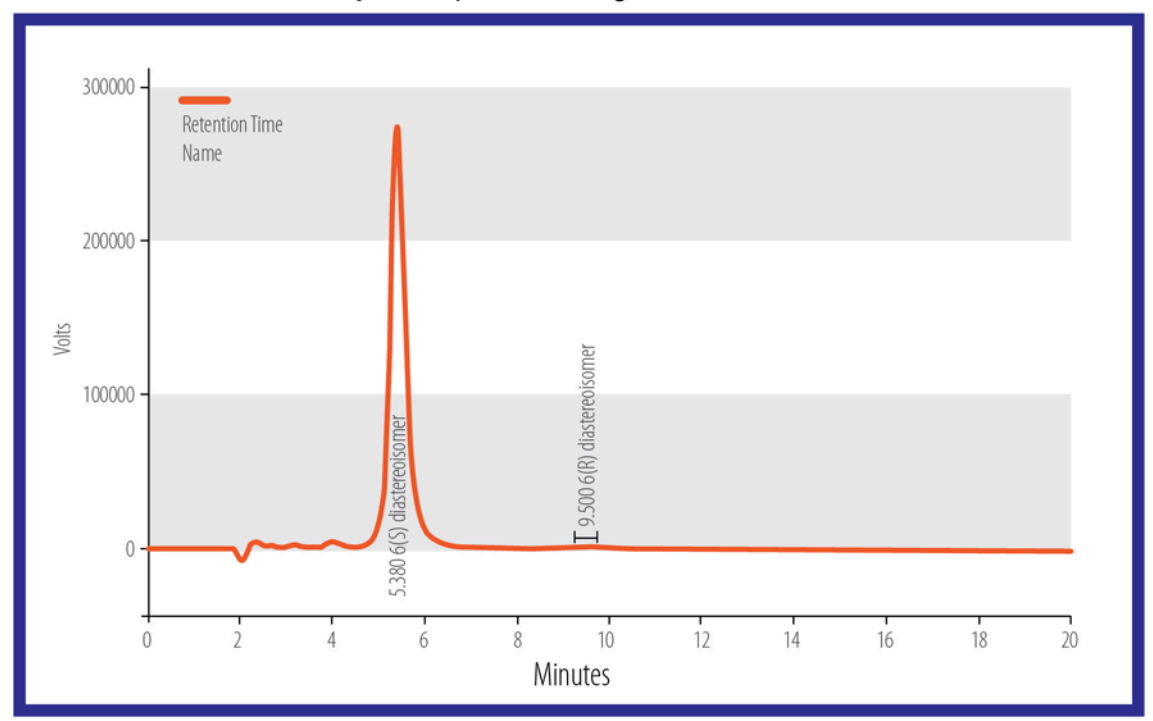
The *novel* purification process of Extrafolate-S[®] is part of Gnosis intellectual property.

The process separates (6S)-5-MTHF from the mixture of two diastereoisomers.

The Green process utilizes a resolving agent in an aqueous environment, in the total absence of organic solvents.

Process for the diastereoisomeric resolution of 5-methyltetrahydrofolic acid."
(PCT/EP2008/52034)

Diastereoisomers HPLC assay – Sample chromatogram



Intellectual Properties

PATENTS:

“Process for the diastereoisomeric resolution of 5-methyltetrahydrofolic acid.”
(PCT/EP2008/52034)

TRADEMARK

Extrafolate® is a proprietary trademark of Gnosis S.p.A.
Registered in USA, EU and Japan.

LEGISLATION AND COMPLIANCE

- NDIN (New Dietary Ingredient) Notification
- GRAS (Generally Recognized as Safe) Self-Affirmation
- Manufacturing Operations FDA Inspected
- HACCP
- 21CFR Part 111

CERTIFICATIONS

- UNI EN ISO 22000:2500

Finished Products on the Market



Supplement Facts:

Each capsule contains:

Folate 5mg (1250%DV)

---[as L-5-Methyltetrahydrofolate, calcium salt]

Other Ingredients: vegetarian capsule.

Contains NO: excipients.

Recommended Use:

Adults: Use only as directed by a health professional.

Warnings:

If you are pregnant, nursing, or taking medications, consult your healthcare professional before using this product. Keep out of the reach of children.



Supplement Facts

Serving Size: 1 Vegetarian Capsule

Servings per Container: 60

	Amount Per Serving	% Daily Value
Folate (as 5-Methyl-tetrahydrofolate)	1000 mcg	250%

Other Ingredients: Microcrystalline cellulose, hypromellose (derived from cellulose) capsule, leucine, silicon dioxide.

Warnings

If pregnant, consult your health-care practitioner before using this product.

Serving Size: 1 capsule

Servings Per Container: 60

Amount Per Serving

Folate ... 5mg

(as L-5-Methyltetrahydrofolate)*

Other Ingredients: Microcrystalline Cellulose, Hypromellose (derived from cellulose) capsule, Leucine, Silicon Dioxide.

This product does not contain wheat, gluten, corn, yeast, soy, egg, dairy products, or artificial colors, artificial sweeteners, or artificial flavors. This product also does not contain lactose, palmitic acid, magnesium stearate, or stearic acid.

