



DOSSIER · SUBSTANCE

Betaine (Trimethylglycine)

Betaine is a naturally occurring **methyl group donor** that has been examined in controlled studies, primarily in **metabolism** and **cardiovascular health**.

The most notable finding: the majority of research assesses **markers** such as homocysteine, rather than clinical endpoints. The evidence base is broad but not always directly translatable to therapeutic applications.

152

STUDIES IN
TOTAL

65

IN HUMANS

35

OF WHICH
CONTROLLED

27

IN ANIMALS

2

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-16

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Betaine (trimethylglycine) at a glance

ORIGIN:

Betaine (trimethylglycine) is a quaternary ammonium derivative of the amino acid glycine that functions as a natural methyl group donor and osmotic protectant in cells. It is produced through the oxidation of choline or obtained directly from the diet, particularly from beetroot, quinoa, spinach, and whole grains. In the body, it is primarily active in the homocysteine-methionine metabolism and is metabolised in the liver and kidneys.

EVIDENCE BASE:

152 evaluated publications · 35 controlled human studies · 30 observational studies · 11 review articles · 27 animal studies · 1 cell culture study

STRONGEST EVIDENCE:

- **Metabolism** Betaine reduces post-methionine load homocysteine levels by 18% in chronic kidney disease without affecting fasting levels. A meta-analysis showed a dose-dependent reduction in homocysteine levels by 1.23 µmol/l at doses of ≥4 g daily.
- **Heart and circulation** Betaine reduces homocysteine levels by up to 12% but shows no significant improvement in endothelial function (FMD) in healthy participants or haemodialysis patients. Observational studies suggest associations between betaine levels and cardiovascular risks.
- **Inflammatory processes** In non-alcoholic steatohepatitis (NASH), betaine (20 g daily) reduces the degree of steatosis without affecting systemic inflammatory markers or fibrosis. In a preclinical study on Alzheimer’s disease, betaine lowered inflammatory markers (IL-1β, TNF-α) and improved cognitive parameters in animal models; these effects have not been investigated in humans.
- **Absorption and bioavailability** Betaine is rapidly absorbed and reduces homocysteine levels in a dose-dependent manner. A daily dose of 3–6 g produces significant effects, while 1 g remains ineffective.
- **Musculoskeletal system** In adolescent handball players, betaine (2.5 g daily) showed enhanced muscular endurance and lowered post-exercise cortisol levels without affecting testosterone levels.

LIMITATIONS:

- Most studies measure surrogate parameters such as homocysteine rather than clinical endpoints (e.g., mortality, disease progression).
- Combinations with other methyl group donors (folic acid, vitamin B12) may complicate the isolation of specific betaine effects.
- Long-term data on safety and efficacy with prolonged supplementation are still limited.

CLASSIFICATION:

Betaine is a well-studied methyl group donor with demonstrated effects on homocysteine metabolism; however, its clinical relevance for cardiovascular disease, inflammatory processes, and metabolic disorders remains inconclusive.

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1. What Betaine Is and How It Works

Betaine (trimethylglycine) is a quaternary ammonium derivative of the amino acid glycine. In the body, betaine functions as an **osmotic protectant** in cells and as a **methyl group donor** in the **homocysteine-methionine metabolism**. This dual role makes it relevant for both basic research and clinical studies, as it can influence **cellular stability** and **epigenetic processes**. Betaine is metabolised in the liver and kidneys and excreted via urine.

For understanding the evidence base, it is crucial to recognise that betaine is studied in two **functionally distinct contexts**: as an **endogenous metabolite** (e.g., in observational studies on cardiovascular disease) and as an **exogenously administered agent** (in controlled intervention studies). **Bioavailability** is high, but **plasma levels** depend heavily on **kidney function**. Additionally, betaine is often combined with other **methyl group donors**, such as folic acid or vitamin B12, which complicates the **isolation of its effects**. Most studies measure **homocysteine** as a **surrogate parameter** rather than clinical outcomes such as disease progression or mortality.

2. What the Studies Show in Detail

The key human studies and major reviews—organised by application area, including population, duration, preparation, measured parameters, and results, as reported in the original publications. Numbers are included only where the study specifies them.

Distribution of **controlled human studies** by application area—the numbers are not additive, as a single study may be assigned to multiple areas:

APPLICATION AREA	CONTROLLED STUDIES
Heart and circulation	12
Safety and tolerability	10
Metabolism	9
Fatigue and stress	6
Musculoskeletal system	3

APPLICATION AREA	CONTROLLED STUDIES
Absorption and bioavailability	3
Gut and microbiome	2
Immune system	2

Inflammatory Processes

In a randomised, placebo-controlled study of 55 patients with biopsy-confirmed non-alcoholic steatohepatitis (NASH), the effect of betaine (20 g daily, oral) was investigated over 12 months. Of the 35 participants who completed the study (17 betaine, 18 placebo), 34 underwent a follow-up biopsy. The betaine group showed a significant reduction in the degree of steatosis but no changes in the NAFLD activity score or fibrosis stage. Inflammatory markers such as insulin, glucose, proinflammatory cytokines, and antioxidant status did not improve. Adiponectin, an anti-inflammatory adipokine, decreased in both groups. S-adenosylhomocysteine, a metabolite of homocysteine metabolism, remained elevated despite betaine administration. The study demonstrates a specific but limited effect on hepatic steatosis without influencing systemic inflammatory parameters or fibrosis ¹.

An observational study in Alzheimer's patients (sample size not explicitly stated) examined the relationship between malnutrition, hyperhomocysteinaemia, and the effects of a dietary betaine intervention. Laboratory analyses showed reductions in phosphorylated tau protein and inhibition of amyloid-β (Aβ) accumulation, alongside significant decreases in inflammatory markers IL-1β and TNF-α. Cognitive status, measured using the ADAS-Cog scale, improved following the intervention. The tau and amyloid findings are derived from preclinical models, and their relevance for human neuroprotection remains untested. Details on participant numbers, intervention duration, and exact dosage are missing from the abstract ³⁰.

A longitudinal multi-omics and microbiome meta-analysis involving 40 adults with experimental gingivitis demonstrated that betaine (as a metabolite in plaque) and *Rothia* species significantly declined during the early phase of gingivitis (24–72 hours after discontinuing oral hygiene). This decline correlated with the activation of 11 salivary cytokines, suggesting a potential association between betaine levels and gingival inflammation. The study defines an asymptomatic, suboptimal health stage (SoH) of the gingiva, which may act as a link between gingivitis, periodontitis, and ageing. The findings are observational and do not establish betaine's causal role in modulating inflammation.

HYPOTHESIS

The available studies suggest that **betaine** may exert modulatory effects in specific inflammatory contexts such as NASH or gingivitis. Whether systemic anti-inflammatory effects occur has yet to be clarified. In particular, studies using standardised inflammation models (e.g., LPS-induced systemic inflammation) and longer intervention periods have yet to be conducted to assess the applicability to chronic inflammatory diseases.

Heart and Circulation

In a randomised, placebo-controlled crossover study involving 39 healthy men and women (aged 50–70 years), the effects of betaine (6 g daily) and folic acid (0.8 mg daily) on endothelial function were investigated over 6 weeks. Betaine reduced fasting homocysteine levels by 12% (–1.2 μmol/l), while folic acid reduced them by 20% (–2.0 μmol/l). However, flow-mediated vasodilation (FMD) of the brachial artery did not improve significantly in either group. The study shows that while betaine lowers homocysteine, it has no direct effect on endothelial function ¹³.

A randomised controlled trial involving 35 haemodialysis patients examined the effects of folic acid (5 mg daily) with or without betaine (4 g daily) over 12 weeks on endothelial function. Despite a rapid reduction in homocysteine levels (from 46.9 ± 6.3 μmol/l to near-normal values in only 2 of 30 patients), no improvement in flow-mediated vasodilation or plasma levels of endothelium-dependent proteins was observed. Betaine had no additional effect compared to folic acid alone. The study suggests that betaine does not influence endothelial dysfunction in end-stage renal disease ².

Supplementation with a combination of substances led to a slight increase in systolic (3.0–5.4 mmHg) and diastolic blood pressure (3.0–3.9 mmHg) compared to the placebo group. QT intervals in the ECG remained unchanged, and no serious adverse events occurred. The study demonstrates that the combination may transiently elevate blood pressure without posing cardiac risks, but the specific contribution of betaine was not examined and remains unclear, as the effects cannot be attributed to betaine alone ²⁷.

HYPOTHESIS

The reduction of homocysteine levels by betaine does not appear to be directly associated with improved endothelial function or cardiovascular outcomes. The effect of betaine on the cardiovascular system may be context-dependent, occurring only in specific patient groups (e.g., those with hyperhomocysteinaemia) or in combination with other therapies. Long-term studies with clinical endpoints such as cardiovascular events or mortality are still pending.

Metabolism

In a randomised crossover study involving 36 patients with chronic kidney disease, the effects of a combination of betaine (4 g daily), folic acid (5 mg), and pyridoxine (50 mg) were investigated over 3 months. The combination reduced post-methionine load homocysteine levels by 18% compared to folic acid and pyridoxine alone (p < 0.001). Fasting homocysteine levels remained unchanged. Slight increases in lipid levels were observed, but the ratio of total to HDL cholesterol did not change. The study confirms that the combination improves homocysteine metabolism following methionine loading in renal insufficiency without affecting fasting levels, though the specific role of betaine in these effects was not determined ³.

A randomised, placebo-controlled study involving 63 healthy participants (mean age 27 ± 8 years) examined the effects of betaine (4 g daily) over 6 months on metabolic parameters. No significant changes in serum lipids (total cholesterol, LDL, HDL, triglycerides) or oxidised LDL were observed. Plasma levels of plasminogen activator inhibitor-1 (PAI-1) increased significantly in the betaine group (p = 0.028), while they decreased in the placebo group (p = 0.006). The study suggests a potential influence of betaine on fibrinolysis but does not demonstrate improvements in metabolic risk factors such as lipids or homocysteine ⁸.

In a randomised study involving 50 healthy participants, the effects of guanidinoacetic acid (GAA, 2.4 g daily) with or without methyl group donors (betaine 1.6 g, vitamin B12, B6, folic acid) were investigated over 8 weeks. The combination with methyl group donors prevented the occurrence of hyperhomocysteinaemia, which developed in 55.6% of participants in the GAA-only group. The study showed that the combination of betaine with other

methyl group donors effectively prevents hyperhomocysteinaemia following GAA administration ¹².

An observational study involving 531 patients with acute coronary syndrome examined the association between betaine levels and secondary events (death, myocardial infarction, heart failure) over a median follow-up of 832 days. Low plasma betaine levels were associated with an increased risk of myocardial infarction ($p = 0.014$), while high levels correlated with an increased risk of heart failure ($p = 0.043$). High dimethylglycine and homocysteine levels were associated with all three endpoints. The study suggests a complex role for betaine in cardiovascular metabolism but does not establish causal mechanisms ²⁹.

HYPOTHESIS Betaine appears to play a role primarily in homocysteine metabolism, particularly under stress conditions such as methionine loading or renal insufficiency. The data on its effects on lipid metabolism or insulin resistance are inconsistent and require further clarification. Studies systematically investigating the influence of betaine on energy metabolism (e.g., mitochondrial function) or its interaction with other methyl group donors are lacking.

Uptake and Availability

In a randomised, double-blind crossover study involving 10 healthy participants (3 men, 7 women; mean age 40.8 ± 12.4 years), the pharmacokinetics of betaine following oral administration of 1, 3, and 6 g were investigated. Betaine led to a dose-dependent increase in serum betaine concentration and a reduction in plasma homocysteine levels. The 3 g and 6 g doses significantly lowered homocysteine levels ($p = 0.019$ and $p < 0.001$, respectively), while the 1 g dose had no effect. The reduction in homocysteine levels correlated linearly with the betaine dose ($p = 0.006$) and serum betaine concentration ($R^2 = 0.17$, $p = 0.025$). The study showed that betaine is rapidly absorbed and dose-dependently lowers homocysteine levels ⁴.

A meta-analysis of five randomised, placebo-controlled studies (2002–2010) involving a total of 195 participants examined the effects of betaine (at least 4 g daily over 6–24 weeks) on homocysteine levels. The pooled effect size showed a significant reduction in homocysteine levels by $1.23 \mu\text{mol/l}$ (95% CI: -1.61 to -0.85 ; $p = 0.01$). The analysis provides evidence that betaine at a dose of at least 4 g daily lowers homocysteine levels ⁷.

HYPOTHESIS The data on the pharmacokinetics and bioavailability of betaine are not well-established, and rapid absorption and a dose-dependent effect on homocysteine levels have not been demonstrated. It remains unclear whether the effect of betaine on homocysteine metabolism depends on individual factors such as gene polymorphisms (e.g., MTHFR) or the presence of metabolic disorders. Studies on long-term availability and potential tolerance development are lacking.

Cognition and Mental Health

In a double-blind, placebo-controlled study involving 48 children with Angelman syndrome, the effects of a combination of betaine and folic acid (dose of betaine not explicitly stated) were investigated over 1 year. No statistically significant changes were observed in the primary endpoints (cognitive, motor, and language development). However, parents of children under 5 years of age reported subjective improvements. The study suggests that the combination has no objectively measurable effects on cognitive development in this population ⁹.

A double-blind, placebo-controlled study involving 73 girls with Rett syndrome examined the effects of a combination of betaine and folic acid over 12 months. No significant changes were observed in the primary endpoints (respiration, hand movements, growth, motor function). The study indicates that the combination has no measurable effects on symptoms in this population ¹⁰.

HYPOTHESIS The available studies on combinations of betaine and folic acid in genetically determined neurological disorders such as Angelman or Rett syndrome show no objectively measurable effects on cognitive or motor development. The influence of betaine on methylation processes in the brain may be too modest to produce clinically relevant changes. Studies investigating the effects of betaine on acquired cognitive impairments (e.g., dementia) or mental health conditions (e.g., depression) are lacking.

Musculoskeletal System

In a randomised, double-blind crossover study involving 10 adolescent handball players (mean age 16 ± 1 years), the effects of betaine (2.5 g daily) over 14 days on muscular endurance and endocrine parameters following acute resistance training were investigated. The study showed a significant increase in the number of repetitions in leg press (betaine: 35.8 ± 4.3 ; placebo: 24.8 ± 3.6 ; Cohen's $d = 2.77$) and bench press (betaine: 36.3 ± 2.6 ; placebo: 26.1 ± 3.5 ; Cohen's $d = 3.34$). Post-exercise cortisol levels were significantly lower in the betaine group (betaine: $7.6 \pm 1.7 \mu\text{g/dl}$; placebo: $13 \pm 3.4 \mu\text{g/dl}$; $p = 0.003$), while testosterone levels remained unchanged. The findings suggest a performance-enhancing effect of betaine and a reduction in post-exercise cortisol levels ¹⁴.

A meta-analysis of six randomised controlled trials involving 195 participants examined the effects of betaine (variable doses) on body composition. The analysis showed a significant reduction in body fat mass (-2.53 kg ; 95% CI: -3.93 to -0.54 kg) and body fat percentage (-2.44% ; 95% CI: -4.20 to -0.68%), without affecting body weight or BMI. The results suggest that betaine may alter body composition in favour of reduced fat mass ¹¹.

HYPOTHESIS The data suggest that betaine may positively influence muscular endurance and body composition, potentially through a reduction in the catabolic hormone cortisol. However, the mechanisms remain unclear, and studies investigating the effects of betaine on muscle protein synthesis or mitochondrial function are lacking. Additionally, the populations studied are often physically active, leaving the applicability to untrained individuals or older adults uncertain.

Overall Picture

The available studies on betaine present a heterogeneous picture, with focal points in homocysteine metabolism, inflammation modulation, and physical performance. The lowering effect of betaine on homocysteine levels is particularly well documented, both in the fasting state and after methionine loading. This effect is dose-dependent and occurs even after short-term supplementation. However, the clinical relevance of this reduction for cardiovascular endpoints or neurological diseases has yet to be investigated. In inflammatory contexts such as non-alcoholic steatohepatitis (NASH) or gingivitis, betaine demonstrates specific but limited effects without influencing systemic inflammatory markers.

The evidence base regarding cognitive or psychological effects of betaine is sparse and shows no objectively measurable benefits in genetically determined neurological disorders. In the musculoskeletal domain, there are indications of performance-enhancing and fat-reducing effects, although long-term studies and mechanistic explanations are lacking. Overall, research on betaine is still in its early stages in many areas, particularly concerning the translatability to clinical endpoints or interactions with other therapies.

Methodology of the evidence base

Studies on betaine encompass a broad spectrum of designs, including randomised, placebo-controlled trials (n = 12), observational studies (n = 5), meta-analyses (n = 2), and review articles (n = 4). The duration of interventions ranged from single acute doses to 12 months, with most studies lasting 6–12 weeks. Typical endpoints included biochemical parameters (homocysteine, lipids, inflammatory markers), physical performance, cognitive function, or histological changes (e.g., liver biopsies). However, studies with clinical endpoints (e.g., cardiovascular events, mortality) and long-term studies on safety and efficacy remain to be conducted. Furthermore, the populations studied are often small and homogeneous (e.g., healthy volunteers or specific patient groups), limiting the generalisability to broader populations.

Homocysteine reduction ≠ clinical benefit

Controlled studies on betaine consistently demonstrate a **REDUCTION IN HOMOCYSTEINE LEVELS**, particularly after methionine loading. Homocysteine is considered a **risk marker** for cardiovascular disease, but the **clinical relevance** of its reduction is **controversial**. Several large intervention studies (e.g., with folic acid) have failed to show a **benefit for myocardial infarction or stroke risk**, despite lowering homocysteine. With betaine, the question arises as to whether the **focus on this marker** is leading research into a **dead end**. A frequently cited study on non-alcoholic fatty liver disease shows **improvements in liver function tests**, but no **hard clinical endpoints** such as fibrosis progression or mortality.

A further issue is the **HETEROGENEITY OF STUDY POPULATIONS**. Many studies examine **patients with renal insufficiency or genetic metabolic disorders**, in whom betaine **acts physiologically differently** than in the general population. The **general applicability** of these results to healthy individuals or other patient groups is therefore **limited**. Additionally, **dose-finding studies** are lacking: most studies use **fixed dosages** without assessing whether these are **optimal**. The **safety** of betaine is considered **well established**, but **long-term data** on potential **adverse effects** (e.g., on lipid metabolism) are **scarce**.

3. How Robust the Research Is

Controlled and observational studies in humans primarily investigate **cardiovascular diseases, metabolic disorders, and safety**. The most frequently cited controlled trials examine betaine in **non-alcoholic fatty liver disease, hyperhomocysteinaemia, and chronic kidney disease**. Observational studies focus on **associations** between betaine levels and **cardiovascular risk factors or inflammatory markers**. Animal and cell studies predominantly explore **molecular mechanisms**, such as the **modulation of inflammatory pathways or epigenetic effects**.

The **methodological robustness** of the studies is **inconsistent**. Controlled trials are often **small and short-term**, with a focus on **laboratory parameters** such as homocysteine or liver enzymes. The **translatability** to clinical endpoints is therefore limited. Observational studies show **associations** but no **causality**—for example, between low betaine levels and increased cardiovascular risk. Furthermore, **long-term data** on safety with prolonged supplementation remain to be collected. The **combination with other methyl group donors** (e.g., folic acid) complicates the **attribution of specific effects**. Research on betaine is **broad**, and the depth needed to derive therapeutic recommendations remains to be clarified.

4. Common Claims—and What the Data Show

CLAIM	EVIDENCE BASE
Betaine in cardiovascular disease	The body of research indicates associations between low betaine levels and increased risk, but no controlled studies with clinical endpoints such as myocar
Betaine in non-alcoholic fatty liver disease (NAFLD)	A frequently cited study demonstrates improvements in liver function tests , but provides no data on fibrosis progression or long-term outcomes .
Betaine in chronic kidney disease	Controlled studies demonstrate a reduction in homocysteine , but no effects on endpoints such as dialysis dependency or mortality.

CLAIM	EVIDENCE BASE
Betaine in neurological disorders (e.g., Angelman syndrome)	Small studies show no significant effects on cognitive or motor functions that would be statistically robust .

5. Profile: Molecule and Charge

Betaine (trimethylglycine) is not a single molecule but a **mixture**—there is no molecular formula or fixed molecular mass. What can be described are functional groups, charge behaviour, and redox properties; these are the focus of the next section.

6. Charge, Electrons, Radicals

Betaine exhibits antioxidant properties in cell cultures by influencing redox signalling pathways. It activates the Nrf2/HO-1 pathway, which reduces the formation of reactive oxygen species (ROS). Concurrently, concentrations of malondialdehyde (MDA), a marker of oxidative stress, decrease, while levels of glutathione (GSH) and glutathione peroxidase 4 (GPX4) increase. These effects suggest involvement in electron transfer processes and radical scavenging. Direct measurements of electrochemical parameters such as charge or cation exchange in human samples are not available. The data are derived from laboratory investigations in cell cultures ²⁰.

In fundamental microbiological studies, betaine has been identified as a substrate for bacterial metabolic processes in which electrons are transferred to acceptors such as nitrate or fumarate. This results in the production of dimethylglycine and CO₂. These observations pertain to anaerobic conditions and are not applicable to humans. Electrochemical properties such as cation exchange or charge behaviour were not examined in these studies. Animal models (cattle) show no direct evidence of redox or radical processes involving betaine but describe changes in bile acid and fatty acid metabolism ^{21 22}.

7. Interactions with Other Substances

Substances with which this compound has been **jointly** investigated or discussed in human studies and review articles—whether in combination, comparison, or via a shared mechanism of action. The number indicates studies in which both appear.

SUBSTANCE	STUDIES IN COMMON	OF WHICH CONTROLLED IN HUMANS
Vitamin B12	25	7
Chronic inflammation	14	3
L-Carnitine	13	2
Gut microbiome	11	1
Magnesium	10	2
Stress, cortisol and inflammation	10	4
Therapeutic fasting and intermittent fasting	10	9
Glycine	9	2
Creatine	8	5
Omega-3 fatty acids	5	1

Betaine may mitigate the development of hyperhomocysteinaemia when administered concurrently with guanidinoacetic acid ¹². An interaction with the MTHFR genotype was examined in a controlled study using dosages of 2.5 and 5.0 g/day, though no concrete enzyme modulation (e.g., CYP) was demonstrated. In animal studies, a combined effect with magnesium, vitamin E, and oleuropein on oxidative parameters was observed, though no specific binding or enzyme interactions were described ^{23 23}. In plants, the betaine antagonist cycloleucine inhibits growth at a concentration of 20 mmol/L, suggesting competitive mechanisms.

Laboratory investigations show that betaine derivatives (e.g., alkylbetainate bromides) can be combined with herbicidal anions, indicating potential interactions with structurally similar substances ²⁴. Whether betaine alters the bioavailability of other nutrients or medications has not been systematically studied. Its effect on the gut barrier and microbiota is mentioned in review articles as an indirect mechanism, though no specific interactions with enzymes or transport proteins have been established.

8. Overdose, Tolerability, and Limitations

In controlled human studies, adverse effects of betaine have been documented, though without consistent dosage specifications. In one study, seven participants experienced serious adverse events, including worsening of seizures, sleep disturbances, constipation, and loss of appetite, leading to study discontinuation ²⁵. Milder adverse events were reported in 33.3% of participants in a group receiving guanidinoacetic acid (GAA) and in 10.0% of those in a group receiving GAA plus methyl group donors (including betaine), though the difference was not statistically significant. In another study combining betaine with S-adenosylmethionine (SAME), fewer side effects were observed compared to other groups ¹⁶. No adverse effects were noted in a study involving betaine-containing preparations in healthy volunteers ²⁸.

Data on the toxicity and overdose of betaine are limited. In a study combining betaine with creatine and a plant extract, no serious adverse events were reported, and tolerability was described as good ^{27 27}. In studies on its use in non-alcoholic fatty liver disease (NASH) or metabolic dysfunction-associated steatotic liver disease (MASLD) with elevated ALT levels, no specific toxicity thresholds were identified, though no safety concerns were raised ^{26 1}. Further investigations into dose-response relationships and long-term safety are warranted.

9. The Most Robust Studies

Ranked by evidential strength, not by prominence. The full evaluation includes significantly more studies; only the most reliable are listed here.

Controlled Human Studies

- ¹ Betaine for nonalcoholic fatty liver disease: results of a randomised placebo-controlled trial (2009)
- Homocysteine: role and implications in atherosclerosis (2006)
- ² No change in impaired endothelial function after long-term folic acid therapy of hyperhomocysteinaemia in haemodialysis patients (1998)
- ³ Betaine supplementation decreases post-methionine hyperhomocysteinaemia in chronic renal failure (2002)
- ⁴ Orally administered betaine has an acute and dose-dependent effect on serum betaine and plasma homocysteine concentrations in healthy humans (2006)
- ⁵ Effect of folic acid and betaine on fasting and postmethionine-loading plasma homocysteine and methionine levels in chronic haemodialysis patients (1999)
- ⁶ Betaine as a determinant of postmethionine load total plasma homocysteine before and after B-vitamin supplementation (2004)
- A therapeutic trial of pro-methylation dietary supplements in Angelman syndrome (2011)
- ⁷ Betaine supplementation decreases plasma homocysteine in healthy adult participants: a meta-analysis (2013)
- ⁸ Long-term effect of betaine on risk factors associated with metabolic syndrome in healthy subjects (2011)
- ⁹ Double-blind therapeutic trial in Angelman syndrome using betaine and folic acid (2010)
- ¹⁰ A study of the treatment of Rett syndrome with folate and betaine (2009)
- Prenatal and postnatal treatment in cobalamin C defect (2005)
- Effects of a pre-workout supplement on lean mass, muscular performance, subjective workout experience and biomarkers of safety (2014)
- ¹¹ Effect of Betaine on Reducing Body Fat—A Systematic Review and Meta-Analysis of Randomised Controlled Trials (2019)
- ¹² Co-administration of methyl donors along with guanidinoacetic acid reduces the incidence of hyperhomocysteinaemia compared with guanidinoacetic acid alone (2013)
- ¹³ Effect of folic acid and betaine supplementation on flow-mediated dilation: a randomised, controlled study in healthy volunteers (2006)
- ¹⁴ Effects of short-term betaine supplementation on muscle endurance and indices of endocrine function following acute high-intensity resistance exercise (2022)
- ¹⁵ Betaine Supplementation Moderately Increases Total Cholesterol Levels: A Systematic Review and Meta-Analysis (2021)
- ¹⁶ Preliminary results of a randomised controlled trial comparing a fixed combination of S-adenosyl-L-methionine and betaine versus amitriptyline (2015)
- ¹⁷ Effects of Two-Week Betaine Supplementation on Apoptosis, Oxidative Stress, and Aerobic Capacity after Exhaustive Endurance Exercise (2020)
- ¹⁸ Effects of low-dose B vitamins plus betaine supplementation on lowering homocysteine concentrations among Chinese adults with hyperhomocysteinaemia: a study (2023)
- ¹⁹ Human Serum Betaine and Associated Biomarker Concentrations Following a 14-Day Supplemental Betaine Loading Protocol and During a 28-Day Washout Period (2022)
- Dimethylglycine supplementation does not affect plasma homocysteine concentrations in pre-dialysis chronic renal failure patients (2004)

10. Summary

Betaine is well established as a methyl group donor in the homocysteine-methionine metabolic pathway. Controlled studies demonstrate a consistent reduction in homocysteine levels, particularly in stress conditions such as methionine loading or renal insufficiency. Bioavailability is high, and dose-dependent effects are documented. In non-alcoholic steatohepatitis (NASH), betaine reduces hepatic steatosis (as shown in liver biopsies) without affecting systemic inflammatory markers or fibrosis. In cardiovascular health, it lowers homocysteine but does not improve endothelial function. Data on its influence on lipid metabolism, insulin resistance, or cognitive function are inconsistent.

HYPOTHESIS Betaine may exert modulatory effects in specific contexts, such as hyperhomocysteinaemia, NASH, or physical exertion. However, the reduction in homocysteine levels does not appear to be directly associated with clinical endpoints. The effect of betaine on the cardiovascular system or inflammatory processes may be context-dependent, manifesting only in certain patient groups or in combination with other therapies. Available data suggest that **betaine** may play a role in inflammatory processes, though systematic investigations in chronic inflammatory diseases remain to be conducted.

Future research should examine clinical endpoints such as cardiovascular events, mortality, or progression of metabolic diseases. Additionally, systematic evaluation of betaine in combination with other methyl group donors or in the context of specific gene polymorphisms (e.g., MTHFR) is needed. Long-term studies on the safety and efficacy of sustained supplementation, as well as investigations into its impact on energy metabolism (e.g., mitochondrial function), are still pending. For cognition and mental health, whether betaine influences acquired disorders such as dementia or depression remains an open question.

11. Unresolved Questions

- **Dose-response relationship:** What is the optimal betaine dose for each indication—and are there **threshold values**?
- **Long-term safety:** Are there **risks** associated with sustained supplementation, such as effects on **lipid metabolism** or **renal function**?
- **Clinical endpoints:** Can **hard outcomes** (e.g., mortality, disease progression) be influenced by betaine—or does its impact remain limited to **surrogate parameters**?

12. Further Paths

Topics, mechanisms and chains in which this substance appears — for those who want to look beyond the substance.

- Interaction network

Frequently Asked Questions

Can betaine safely lower homocysteine—and is this therapeutically relevant?

Controlled studies demonstrate that betaine **lowers homocysteine**, particularly following methionine loading. However, whether this reduction is **clinically relevant** remains unclear. Large studies involving other methyl group donors (e.g., folic acid) have **failed to show benefits for cardiovascular endpoints**, despite homocysteine reduction. Betaine may therefore be **merely a marker** rather than a **therapeutic target**.

Are there risks associated with betaine supplementation?

Betaine is considered **safe** within the studied dosage ranges. Most trials report **no severe adverse effects**, though **long-term data** on potential impacts on **lipid metabolism** or **renal function** are lacking. In cases of **renal insufficiency**, betaine should be used **with caution**, as **excretion** may be impaired. **Interactions** with other methyl group donors (e.g., folic acid) are **possible** but have not been systematically investigated.

Can betaine be used in non-alcoholic fatty liver disease (NAFLD)?

One controlled study shows **improvements in liver function tests** with betaine supplementation. However, **data on hard endpoints**, such as **fibrosis progression** or **long-term outcomes**, are lacking. The evidence is **insufficient** to recommend betaine as a **standard therapy** for NAFLD. Further research with **clinical endpoints** is required.

Sources

- 1 Betaine for nonalcoholic fatty liver disease: results of a randomized placebo-controlled trial
Abdelmalek MF, Sanderson SO, Angulo P, Soldevila-Pico C, Liu C, Peter J et al. · 2009
- 2 No change in impaired endothelial function after long-term folic acid therapy of hyperhomocysteinemia in haemodialysis patients
van Guldener C, Janssen MJ, Lambert J, ter Wee PM, Jakobs C, Donker AJ et al. · 1998
- 3 Betaine supplementation decreases post-methionine hyperhomocysteinemia in chronic renal failure
McGregor DO, Dellow WJ, Robson RA, Lever M, George PM, Chambers ST · 2002
- 4 Orally administered betaine has an acute and dose-dependent effect on serum betaine and plasma homocysteine concentrations in healthy humans
Schwab U, Törrönen A, Meririnne E, Saarinen M, Alfthan G, Aro A et al. · 2006
- 5 Effect of folic acid and betaine on fasting and postmethionine-loading plasma homocysteine and methionine levels in chronic haemodialysis patients
van Guldener C, Janssen MJ, de Meer K, Donker AJ, Stehouwer CD · 1999
- 6 Betaine as a determinant of postmethionine load total plasma homocysteine before and after B-vitamin supplementation
Holm PI, Bleie Ø, Ueland PM, Lien EA, Refsum H, Nordrehaug JE et al. · 2004
- 7 Betaine supplementation decreases plasma homocysteine in healthy adult participants: a meta-analysis
McRae MP · 2013
- 8 Long-term effect of betaine on risk factors associated with the metabolic syndrome in healthy subjects
Schwab U, Alfthan G, Aro A, Uusitupa M · 2011
- 9 Double-blind therapeutic trial in Angelman syndrome using betaine and folic acid
Peters SU, Bird LM, Kimonis V, Glaze DG, Shinawi LM, Bichell TJ et al. · 2010
- 10 A study of the treatment of Rett syndrome with folate and betaine
Glaze DG, Percy AK, Motil KJ, Lane JB, Isaacs JS, Schultz RJ et al. · 2009
- 11 Effect of Betaine on Reducing Body Fat-A Systematic Review and Meta-Analysis of Randomized Controlled Trials
Gao X, Zhang H, Guo XF, Li K, Li S, Li D · 2019
- 12 Co-administration of methyl donors along with guanidinoacetic acid reduces the incidence of hyperhomocysteinemia compared with guanidinoacetic acid administration alone
Ostojic SM, Niess B, Stojanovic M, Obrenovic M · 2013
- 13 Effect of folic acid and betaine supplementation on flow-mediated dilation: a randomized, controlled study in healthy volunteers
Olthof MR, Bots ML, Katan MB, Verhoef P · 2006
- 14 Effects of short-term betaine supplementation on muscle endurance and indices of endocrine function following acute high-intensity resistance exercise in young athletes
Arazi H, Aboutaleb S, Taati B, Cholewa JM, Candow DG · 2022
- 15 Betaine Supplementation Moderately Increases Total Cholesterol Levels: A Systematic Review and Meta-Analysis
Zawieja EE, Zawieja B, Chmurzynska A · 2021
- 16 Preliminary results of a randomized controlled trial carried out with a fixed combination of S-adenosyl-L-methionine and betaine versus amitriptyline in patients with mild depression
Di Pierro F, Settembre R · 2015
- 17 Effects of Two-Week Betaine Supplementation on Apoptosis, Oxidative Stress, and Aerobic Capacity after Exhaustive Endurance Exercise
Yang MT, Lee XX, Huang BH, Chien LH, Wang CC, Chan KH · 2020
- 18 Effects of low-dose B vitamins plus betaine supplementation on lowering homocysteine concentrations among Chinese adults with hyperhomocysteinemia: a randomized, double-blind, controlled preliminary clinical trial
Lu XT, Wang YN, Mo QW, Huang BX, Wang YF, Huang ZH et al. · 2023
- 19 Human Serum Betaine and Associated Biomarker Concentrations Following a 14 Day Supplemental Betaine Loading Protocol and during a 28 Day Washout Period: A Pilot Investigation
Machek SB, Zawieja EE, Heilesen JL, Harris DR, Wilburn DT, Fletcher EA et al. · 2022
- 20 BET upregulates nuclear factor E2-related factor 2/heme oxygenase 1 (Nrf2/HO-1) signaling, reducing long-chain acyl-CoA ...
· 2026
- 21 D. hafniense was found capable of growth on glycine betaine with electron acceptors such as nitrate or fumarate, produci...
· 2014
- 22 Notably, cows fed high grain diet had higher serum concentrations of primary bile acids and triglycerides, but lower lev...
· 2020
- 23 This study evaluates the effect of the dietary combination of oleuropein extract (1200 mg/kg) and betaine (1000 mg/kg), ...
· 2021
- 24 After esterification, the obtained alkyl betainate bromides containing straight alkyl chains varying from ethyl to octad...
· 2020
- 25 There were 10 adverse events that resulted in study withdrawal of 7 participants (worsening of seizures, onset, or worse...
· 2011
- 26 Our aim was to determine the safety and efficacy of lower doses of betaine in clinically diagnosed metabolic dysfunction...
· 2026
- 27 In this prospective, randomized, double-blind, trial conducted in two parts, we examined the effects of a multi-ingredie...
· 2014
- 28 No side effects were observed in either treatment group....
· 2016
- 29 Betaine and secondary events in an acute coronary syndrome cohort
Lever M, George PM, Elmslie JL, Atkinson W, Slow S, Molyneux SL et al. · 2012
- 30 Association between malnutrition and hyperhomocysteine in Alzheimer's disease patients and diet intervention of betaine
Sun J, Wen S, Zhou J, Ding S · 2017

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