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Betaine (TMG) as a Dietary Supplement in Sports – Mechanisms of Action, Ergogenic Effects, and Safety of Use

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Abstract
Betaine supplementation is gaining popularity as a strategy to enhance physical performance, particularly in strength and endurance training. Although large-scale, multicenter studies remain limited, available evidence suggests potential ergogenic benefits such as improved lower-body strength and jump performance. Supplementation may also influence hormonal balance by increasing the testosterone-to-cortisol ratio, promoting an anabolic state. Findings regarding betaine's impact on body composition remain mixed—some studies report no significant changes in lean mass or fat mass, while others suggest a reduction in fat mass without changes in overall body weight. The proposed mechanisms include increased intramuscular betaine concentration and osmotic activity, which may support recovery and protect muscle cells. Despite promising results, further well-designed clinical trials are needed to evaluate different populations, dosing protocols, and the long-term safety of supplementation. This review synthesizes the current body of knowledge and offers recommendations for future research and practical applications of betaine in sports.

Keywords: betaine, trimethylglycine, supplementation, sport, muscle strength, physical performance, body composition, oxidative stress.

1. Introduction

Traditional supplements used in sports, such as creatine and beta-alanine, continue to dominate the market. Betaine, primarily known for its role in cytoprotection and homocysteine methylation, has recently gained attention for its potential ergogenic properties. Its multifaceted effects—including osmotic regulation, methylation activity, and anabolic potential—make it a promising aid for both strength and endurance training. The aim of this paper is to provide a comprehensive review of the mechanisms of action, physiological effects, safety profile, and practical recommendations regarding the use of betaine in a sports context.

2. Chemical Characteristics, Bioavailability, and Metabolism

Betaine (trimethylglycine, TMG) is a natural derivative of glycine containing three methyl groups attached to a nitrogen atom. Its molecular formula is $C_5H_{11}NO_2$, and its chemical structure represents a zwitterionic form of a quaternary ammonium salt. It is widely found in plants, animals, and microorganisms, with some of the richest dietary sources including sugar beets, spinach, wheat bran, cereal sprouts, and certain aquatic invertebrates [1]. Betaine can be synthesized endogenously from choline through oxidation to betaine aldehyde and subsequently to betaine proper, or it can be supplied exogenously through the diet [2][3]. After ingestion, betaine is absorbed in the small intestine, likely involving transporters from the solute carrier family, such as SIT1 (SLC6A20) [4][5]. It then travels to the liver and kidneys, where it is transported by BGT-1 (SLC6A12) [6][7]. The main metabolic pathway involves betaine-homocysteine methyltransferase, which catalyzes the transfer of a methyl group to homocysteine, resulting in the regeneration of methionine and formation of dimethylglycine. Dimethylglycine is further metabolized to sarcosine and then to glycine; these reactions primarily occur in the mitochondria of hepatic and renal cells [8][9][10]. Due to its ability to donate methyl groups, betaine plays a key role in the methionine cycle and in the biosynthesis of S-adenosylmethionine (SAM), the principal methyl donor in methylation reactions [11]. These metabolites are involved in numerous physiological processes such as the biosynthesis of creatine, phospholipids, neurotransmitters, and DNA methylation [12][13]. Additionally, betaine acts as an osmoprotectant—stabilizing proteins and cell membranes under osmotic stress—thus supporting the structural integrity of muscle cells during intense physical exertion [14][15]. From an industrial perspective, betaine is available in three forms: natural anhydrous betaine, synthetic anhydrous betaine, and betaine hydrochloride [16]. The natural form, most commonly extracted from sugar beets, exhibits superior functional properties and is preferred in pharmaceutical, cosmetic, and supplement industries [17]. In the United States, betaine has been granted GRAS status (Generally Recognized as Safe), while in the European Union its use has been approved by the European Commission with a recommended minimum amount of 500 mg per serving of food product [18].

3. Mechanisms of Action in the Sports Context

3.1. Methyl Donor and Support for Creatine Synthesis

Betaine, as a potent methyl group donor, plays a crucial role in one of the key metabolic pathways responsible for creatine synthesis, which is a vital energy substrate for muscles during short-term, high-intensity physical efforts [8][19]. In the body, betaine donates its methyl groups to homocysteine in a reaction catalyzed by the enzyme betaine-homocysteine methyltransferase (BHMT), leading to the regeneration of methionine [20]. Methionine is then converted into S-adenosylmethionine (SAM)—a universal methyl donor in numerous methylation reactions, including those related to creatine synthesis [11]. Creatine synthesis primarily occurs in the kidneys and liver, where guanidinoacetate formed from arginine and glycine is methylated by SAM to produce creatine. Creatine plays a fundamental role in regenerating ATP via the phosphocreatine system in muscles, enabling the maintenance of high-intensity anaerobic effort and accelerating energy recovery between exercise sets [21][22]. Supplementation with betaine increases the availability of methionine and SAM, potentially enhancing endogenous creatine synthesis, thereby improving exercise capacity and muscle recovery [23]. Additionally, by increasing SAM levels, betaine may influence the activation of the mTOR (mammalian Target of Rapamycin) pathway—a key regulator of muscle protein synthesis and anabolic processes [24]. Activation of mTOR stimulates mRNA translation, leading to increased muscle protein synthesis, supporting hypertrophy and post-exercise recovery [25]. Both in vitro and in vivo studies have demonstrated that betaine supplementation can increase the expression of proteins involved in anabolic signaling and improve muscle mass and strength [21][26]. Thus, by supporting methylation and the mTOR pathway, betaine acts comprehensively, enhancing both energy availability (via creatine synthesis) and stimulating muscle repair and growth processes.

3.2. Osmoprotection and Cellular Hypertrophy

Betaine serves an important function as an osmoprotectant, a compound that helps maintain water-electrolyte homeostasis in cells under osmotic stress. During intense physical exercise, especially under conditions of dehydration or elevated extracellular ion concentrations, muscle cells are exposed to water loss, which can lead to impaired cellular function and inhibition of anabolic processes. Betaine accumulates within cells, causing an increase in their volume—known as cellular hypertrophy—which itself acts as a strong anabolic signal [27][28]. Cell swelling activates the mTOR (mechanistic Target of Rapamycin) pathway, a central regulator of muscle protein synthesis and muscle mass growth. Activation of mTOR enhances mRNA translation into proteins, resulting in increased muscle protein synthesis and supporting hypertrophy and post-exercise recovery [29]. Furthermore, betaine reduces osmotic stress by protecting proteins and cell membranes from denaturation and damage, helping to maintain cell integrity and optimal muscle function during exercise [30]. By reducing oxidative stress and stabilizing enzymes, betaine also supports muscle recovery and decreases muscle damage. Studies in cellular and animal models have confirmed that betaine supplementation increases levels of mTOR and its downstream effectors, such as p70S6K, which are directly associated with improvements in muscle mass and strength [31]. Clinical studies have observed that betaine supplementation in athletes delays fatigue and improves performance, which may be indirectly related to enhanced osmotic protection and support of muscle hypertrophy [32].

3.3. Oxidative Stress and Recovery

Intense physical exercise leads to increased production of reactive oxygen species (ROS), which can cause damage to muscle cells through lipid peroxidation, protein oxidation, and DNA damage. Oxidative stress is a key factor contributing to muscle fatigue, delayed recovery, and the formation of muscle microtraumas. Betaine exhibits antioxidant properties by reducing oxidative stress through protecting cellular structures from ROS-induced damage. Studies in animal and human models have shown that betaine supplementation lowers levels of muscle damage markers such as creatine kinase (CK) and malondialdehyde (MDA)—a product of lipid peroxidation [33][34]. The reduction of these markers indicates decreased damage to cell membranes and lipids, translating into better protection of muscle tissue. Additionally, betaine supports mitochondrial function—key organelles responsible for energy production in the form of ATP. By stabilizing mitochondrial membranes and supporting redox processes, betaine can improve cellular respiration efficiency and reduce ROS production within mitochondria [8]. Improved mitochondrial function accelerates energy recovery post-exercise, reduces fatigue, and promotes faster muscle repair. Clinical studies in athletes supplementing with betaine observed shortened recovery times and reduced muscle soreness following intense training sessions [29]. This mechanism is likely related to betaine's antioxidant action and mitochondrial protection, which together contribute to the reduction of inflammation and oxidative stress after exercise.

3.4. Muscle Strength and Power

Betaine is an increasingly studied supplement for its ergogenic potential in improving muscle strength and power, which is particularly important for athletes in strength and power-endurance sports. In a recently published meta-analysis by Zawieja et al. which included 17 randomized controlled trials, betaine supplementation was shown to lead to a significant increase in maximal strength measured by the standardized mean difference (SMD = 0.47; $p < 0.05$). This effect was especially pronounced in exercises involving the lower body, such as squats and deadlifts. The authors suggest that betaine may enhance muscle energy reserves and support anabolic processes, resulting in improved strength performance [25]. The study by Hoffman et al. confirmed the ergogenic effect of betaine at a standard dose of 2.5 g per day. Supplementation significantly increased one-repetition maximum strength (1RM) and average power during compound exercises such as the bench press. The authors also highlighted that betaine stimulated the neuromuscular system, which may have contributed to improved motor unit recruitment and muscle contraction efficiency [23]. In the study by Lee et al. (2010), a notable improvement in muscle power during the power clean exercise and increased isometric strength were also observed in participants supplemented with betaine. The authors indicated that betaine's mechanisms of action might be related to its role as a methyl group donor supporting creatine synthesis—a key rapid ATP source during anaerobic exercise—as well as its osmoprotective properties, which increase muscle cell volume and hydration, thereby promoting hypertrophy and enhancing muscle function [22]. In summary, available research indicates that betaine supplementation at approximately 2.5 g per day can significantly improve maximal strength and muscle power, particularly in exercises involving large muscle groups. These effects have practical relevance for athletes training in strength, speed, and endurance disciplines.

3.5. Aerobic Performance

The effect of betaine on aerobic capacity and exercise performance under aerobic conditions is a topic of growing interest in the scientific community. Although betaine is most commonly associated with improvements in muscle strength and power, its potential to support aerobic endurance has also been investigated. Armstrong et al. conducted a study on a group of athletes supplemented with betaine during exercise under conditions of high heat stress and dehydration. The authors observed that despite no significant changes in maximal oxygen uptake (VO_2max), betaine supplementation significantly prolonged time to exhaustion. These results suggest that betaine may improve heat stress tolerance and increase the body's ability to maintain exercise intensity in challenging environmental conditions, which is particularly relevant for endurance sports performed in high temperatures [35]. Trepanowski et al. examined the effect of betaine on microcirculation and tissue oxygenation during intense endurance training. They found that betaine supplementation significantly increased muscle tissue oxygen saturation during exercise, which may translate into better oxygen utilization by muscles and delayed fatigue. The mechanism behind this effect may be related to improved osmotic balance and protection of mitochondria against oxidative stress, thereby enhancing cellular respiration efficiency [36]. Additionally, research suggests that betaine, through its osmoprotective properties, may counteract dehydration of muscle cells during exercise, which is important for maintaining ion homeostasis and enzymatic functions involved in aerobic metabolism [21]. This supports better maintenance of aerobic capacity and faster recovery between training sets. In summary, although betaine does not directly affect VO_2max, its supplementation may improve exercise endurance by increasing time to exhaustion and enhancing muscle oxygenation, especially under conditions of heat stress and dehydration. These effects have significant implications for endurance athletes and competitors training in challenging environmental conditions.

3.6 Body Composition

The effect of betaine supplementation on body composition, particularly on lean body mass and fat mass reduction, has been the subject of numerous studies, although the results vary depending on the population studied and the type of training. Cholewa et al. conducted a study on a group of resistance-trained athletes, in which betaine supplementation for six weeks resulted in a significant increase in lean body mass alongside a concurrent reduction in body fat percentage. The study also demonstrated elevated levels of IGF-1 (insulin-like growth factor 1) and leptin—hormones associated with muscle anabolism and regulation of energy metabolism [31]. These results suggest that betaine may support anabolic processes and promote a favorable shift in muscle-to-fat ratio, which is crucial for athletes aiming to improve body composition. Conversely, a 2019 meta-analysis including studies on physically inactive populations did not confirm a definitive effect of betaine on body composition. The authors noted that in sedentary individuals, betaine supplementation did not produce significant changes in muscle mass or fat tissue, indicating that betaine's effects may depend on physical activity levels and the type of training [37]. More recent research conducted by Zawieja and colleagues (2024) confirmed the beneficial effect of betaine on body composition in strength-trained athletes. A meta-analysis of 17 studies showed that betaine supplementation contributed to an increase in lean body mass and a reduction in fat mass, with these effects being more pronounced in groups engaged in regular resistance training [25]. In summary, betaine may support improvements in body composition, especially when combined with physical activity and strength training. Its anabolic action and influence on growth-related hormones favor muscle mass development, while the effect on fat reduction may be indirectly linked to enhanced metabolism and energy balance.

3.7 Recovery and Oxidative Stress

Betaine supplementation demonstrates beneficial properties in reducing oxidative stress and improving muscle recovery after intense physical exercise. Oxidative stress, resulting from increased production of reactive oxygen species (ROS), is one of the main causes of muscle cell damage and delayed post-training recovery. Durkalec-Michalski and colleagues conducted a study on a group of athletes, showing that 14 days of betaine supplementation led to a significant reduction of creatine kinase (CK) levels by approximately 20% after exercise. Creatine kinase is a marker of muscle damage, and its reduction indicates less severe micro-injuries to the muscles and a faster return to baseline status [38]. This decrease in CK levels translates into better performance and reduced perception of fatigue after exercise. Furthermore, a meta-analysis of randomized trials by Xu et al. demonstrated that betaine supplementation also lowers other markers of inflammation and oxidative stress, such as C-reactive protein (CRP), interleukin-6 (IL-6), and malondialdehyde (MDA)—a product of lipid peroxidation. The reduction of these markers indicates decreased inflammation and protection of cell membranes against oxidative damage [39]. Therefore, betaine may support faster muscle recovery, reduce post-exercise soreness and swelling, which is especially important for athletes engaging in intense training or competing with short rest intervals between efforts. The mechanism of betaine's action in this context includes its ability to stabilize cell membranes and improve mitochondrial function, thereby limiting ROS production and minimizing their destructive impact on muscle tissue. Additionally, betaine may indirectly support antioxidant enzymatic systems, such as glutathione peroxidase, which helps maintain redox homeostasis in muscle cells. In summary, betaine as a dietary supplement not only improves athletic performance but also plays a significant role in protecting muscles from oxidative damage and accelerating recovery after exercise, making it a valuable aid for physically active individuals.

3.8 Applications in Team Sports and Intense Training

Betaine supplementation is gaining popularity in team sports as well as in the context of intense, demanding strength and endurance training. Betaine acts through mechanisms that support recovery, improve hormonal balance, and partially enhance anaerobic capacity, which is particularly important in sports requiring repeated, short, and intense efforts. A study conducted on CrossFit athletes (3 weeks, 2.5–5 g betaine daily) showed a reduction in homocysteine levels and an increase in testosterone levels, while having no significant effect on direct markers of anaerobic power [40]. This suggests that betaine primarily supports metabolic and hormonal processes, which may translate into long-term improvements in recovery and training adaptation. In a study on young soccer players (14-week supplementation), improvements were observed in anaerobic capacity tests and a beneficial change in the testosterone/cortisol ratio, indicating a reduction in metabolic stress and a predominance of anabolic over catabolic processes [26]. Improvement in this ratio is significant because training loads in team sports often lead to increased catabolism, which lowers recovery efficiency and increases the risk of overtraining. Additionally, another study by Cholewa et al. on strength-trained men demonstrated that betaine supplementation (2.5 g/day for 6 weeks) increased maximal strength and muscular endurance, which is important during prolonged, demanding training sessions typical of team sports and heavy training [31]. The authors noted that this effect was related to improved water balance and osmoprotection, which help protect muscle cells from damage during intense exercise. Furthermore, betaine supplementation was found to positively influence immune system parameters and reduce inflammatory markers (e.g., CRP and IL-6) in athletes performing intense interval training, promoting faster recovery and reducing muscle fatigue [26][39]. Mechanistically, betaine serves as a methyl group donor in the methionine cycle, which among other functions enables the reduction of homocysteine—a compound associated with oxidative stress and muscle damage. Additionally, its osmoprotective action helps stabilize cell membranes.

4. Dosage

Betaine (TMG) is typically used at a dose of 2–2.5 g per day for a period of 1–6 weeks, which in numerous studies has been shown to improve muscle performance and recovery. For example, Varanoske et al. reported that after just 7 days of betaine supplementation, an increase in lean body mass and a reduction in fat mass were observed in resistance-trained individuals. Pharmacokinetic studies confirm that doses ranging from 1 to 6 g/day result in elevated betaine concentrations in blood and muscle tissue, as well as a significant reduction in homocysteine levels within 2 hours of administration [23][41][42]. In comparison, in the treatment of homocystinuria, doses as high as 6–9 g/day are often used, typically divided into two daily doses (e.g., 3 g in the morning and 3 g in the evening), without significant adverse effects in most patients. Clinical data demonstrate that long-term use (average of 7 years) of 6 g/day in homocystinuria was well tolerated and effectively reduced homocysteine by an average of 29% [43][44]. The European Medicines Agency also approves the use of 6 g/day for treating the disease, recommending monitoring of blood methionine levels [45]. In the sports context, oral betaine intake is recommended once daily, preferably with a carbohydrate-containing meal, which increases insulin sensitivity and the efficiency of transport to muscles [46]. In training interventions, supplementation is typically started 7–14 days prior to an intense training period or testing, allowing for increased intracellular betaine concentration, enhanced osmoprotective effect, and metabolic support of muscles [25]. Long-term supplementation at a dose of 2.5 g/day for 6–10 weeks also supports increases in lean muscle mass and reductions in fat mass when combined with resistance training. Numerous interventions confirm that these doses are well tolerated and demonstrate metabolic and performance benefits while maintaining safety.

Although doses above 4 g/day are considered safe, they are rarely used in sports without medical consultation due to a lack of necessity and higher cost [47].

5. Safety and Adverse Effects

Betaine supplementation is widely recognized as safe for both healthy athletes and clinical populations. The European Food Safety Authority (EFSA) has stated that betaine, as a novel food, is safe at doses up to 6 mg/kg body weight per day, which corresponds to approximately 400 mg/day for a person weighing 70 kg [48]. However, numerous clinical studies involving individuals taking betaine doses ranging from 2.5 g to 6 g per day have reported no serious adverse effects or disturbances in hematological or biochemical parameters during supplementation periods of up to 6 months [49]. The most commonly reported minor side effects are mild gastrointestinal symptoms such as nausea, bloating, or diarrhea, especially at higher doses (>4–6 g/day), though these are generally transient and self-limiting. Use of specific forms of betaine, e.g., betaine hydrochloride (BHCl), may slightly increase the risk of gastric discomfort, although such reports are rare [50]. Some studies indicate that betaine supplementation at doses ≥4 g/day for at least 3 weeks may lead to a slight increase in LDL cholesterol levels, particularly in populations with overweight or metabolic syndrome. Reviews published by EFSA and the Schwab et al. (2011) report confirm that no significant lipid changes were observed in healthy individuals, but small LDL elevations may occur in those with metabolic disorders [49][51]. Therefore, in individuals with hyperhomocysteinemia, lipid disorders, or kidney diseases, betaine supplementation (above 4 g/day) should be preceded by medical consultation to monitor lipid profiles as well as liver and kidney function. Meanwhile, doses ≤4 g/day for up to 6 months are well tolerated and generally safe in healthy individuals.

6. Conclusions and Recommendations

Betaine supplementation represents a promising strategy for enhancing sports performance, particularly in strength and endurance training, although the available literature indicates a limited number of large, multicenter studies. A meta-analysis by Zawieja et al. (2024), including 17 studies with 317 participants, demonstrated a significant ergogenic effect on lower limb strength and jumping ability (SMD = 0.47), suggesting potential benefits from long-term training interventions [25]. Another study observed a substantial improvement in the testosterone-to-cortisol (T/C) ratio during the competitive season in young soccer players, indicating support for anabolic-catabolic balance [26]. Regarding body composition, results are mixed: a meta-analysis by Ashtary-Larky et al. did not confirm a significant effect of betaine on lean body mass or fat reduction in general populations [52]. Conversely, an earlier systematic review suggested a possible fat mass reduction of approximately 2.5 kg while maintaining body weight [53]. Regular betaine supplementation may support recovery by increasing betaine concentrations in muscles and through its osmotic action, which, combined with training, promotes lean mass growth and protects muscle cells. Improvement in the T/C ratio and reduction of oxidative stress markers such as homocysteine provide additional support to the hormonal and metabolic systems, although the mechanisms underlying these effects require further investigation. Despite promising observations, there is an urgent need for randomized controlled trials with greater statistical power, including women, various training levels, and different sports disciplines. This will allow precise determination of effective dosing protocols, long-term safety, and possible interactions of betaine with other supplements.

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References:
[1] Day CR, Kempson SA. Betaine chemistry, roles, and potential use in liver disease. Biochim Biophys Acta. 2016 Jun;1860(6):1098-106. doi: 10.1016/j.bbagen.2016.02.001. Epub 2016 Feb 2. PMID: 26850693.
[2] Mahmoud Alagawany, Shaaban S. Elnesr, Mayada R. Farag, Karima El-Naggar, Ayman E. Taha, Asmaa F. Khafaga, Mahmoud Madkour, Heba M. Salem, Amira M. El-Tahan, Mohamed T. El-Saadony, Mohamed E. Abd El-Hack, Betaine and related compounds: Chemistry, metabolism and role in mitigating heat stress in poultry, Journal of Thermal Biology, Volume 104, 2022, 103168.
[3] Zhi-Jun Yang, Si-Yu Huang, Jin Cheng, Ji-Wu Zeng, Maierhaba Wusiman, Hua-Bin Li, Hui-Lian Zhu,Betaine: A comprehensive review on dietary sources, health benefits, mechanisms of action, and application, Trends in Food Science & Technology, Volume 159, 2025,104993, ISSN 0924-2244,
[4] Bröer S, Palacín M. The role of amino acid transporters in inherited and acquired diseases. Biochem J. 2011 Jun 1;436(2):193-211. doi: 10.1042/BJ20101912. PMID: 21568940.
[5] Takanaga H, Mackenzie B, Suzuki Y, Hediger MA. Identification of mammalian proline transporter SIT1 (SLC6A20) with characteristics of classical system imino. J Biol Chem. 2005 Mar 11;280(10):8974-84. doi: 10.1074/jbc.M413027200. Epub 2005 Jan 4. PMID: 15632147.
[6] Kempson SA, Vovor-Dassu K, Day C. Betaine transport in kidney and liver: use of betaine in liver injury. Cell Physiol Biochem. 2013;32(7):32-40. doi: 10.1159/000356622. Epub 2013 Dec 18. PMID: 24429813.
[7] Zhou Y, Holmseth S, Hua R, Lehre AC, Olofsson AM, Poblete-Naredo I, Kempson SA, Danbolt NC. The betaine-GABA transporter (BGT1, slc6a12) is predominantly expressed in

the liver and at lower levels in the kidneys and at the brain surface. Am J Physiol Renal Physiol. 2012 Feb 1;302(3):F316-28. doi: 10.1152/ajprenal.00464.2011. Epub 2011 Nov 9. PMID: 22071246.
[8] Craig SA. Betaine in human nutrition. Am J Clin Nutr. 2004 Sep;80(3):539-49. doi: 10.1093/ajcn/80.3.539. PMID: 15321791.
[9] Juliana Pérez-Miguelsanz, Néstor Vallecillo, Francisco Garrido, Edel Reytor, Dolores Pérez-Sala, María A. Pajares, Betaine homocysteine S-methyltransferase emerges as a new player of the nuclear methionine cycle, Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, Volume 1864, Issue 7, 2017, Pages 1165-1182, ISSN 0167-4889
[10] McGregor DO, Dellow WJ, Robson RA, Lever M, George PM, Chambers ST. Betaine supplementation decreases post-methionine hyperhomocysteinemia in chronic renal failure. Kidney Int. 2002 Mar;61(3):1040-6. doi: 10.1046/j.1523-1755.2002.00199.x. PMID: 11849459.
[11] Dobrijević D, Pastor K, Nastić N, Özogul F, Krulj J, Kokić B, Bartkiene E, Rocha JM, Kojić J. Betaine as a Functional Ingredient: Metabolism, Health-Promoting Attributes, Food Sources, Applications and Analysis Methods. Molecules. 2023 Jun 17;28(12):4824. doi: 10.3390/molecules28124824. PMID: 37375378; PMCID: PMC10302777.
[12] Chen, R.; Song, Y.; Yang, M.; Wen, C.; Liu, Q.; Zhuang, S.; Zhou, Y. Effect of Dietary Betaine on Muscle Protein Deposition, Nucleic Acid and Amino Acid Contents, and Proteomes of Broilers. Animals 2022, 12, 736. https://doi.org/10.3390/ani12060736
[13] Lauinger, L.; Kaiser, P. Sensing and Signaling of Methionine Metabolism. Metabolites 2021, 11, 83. https://doi.org/10.3390/metabo11020083
[14] Garrett Q, Khandekar N, Shih S, Flanagan JL, Simmons P, Vehige J, Willcox MD. Betaine stabilizes cell volume and protects against apoptosis in human corneal epithelial cells under hyperosmotic stress. Exp Eye Res. 2013 Mar;108:33-41. doi: 10.1016/j.exer.2012.12.001. Epub 2012 Dec 12. PMID: 23246691.
[15] Ratriyanto A, Mosenthin R. Osmoregulatory function of betaine in alleviating heat stress in poultry. J Anim Physiol Anim Nutr (Berl). 2018 Dec;102(6):1634-1650. doi: 10.1111/jpn.12990. Epub 2018 Sep 20. PMID: 30238641.
[16] Dobrijević D, Pastor K, Nastić N, Özogul F, Krulj J, Kokić B, Bartkiene E, Rocha JM, Kojić J. Betaine as a Functional Ingredient: Metabolism, Health-Promoting Attributes, Food Sources, Applications and Analysis Methods. Molecules. 2023 Jun 17;28(12):4824. doi: 10.3390/molecules28124824. PMID: 37375378; PMCID: PMC10302777.
[17] Awad WA, Ruhnau D, Gavrău A, Dublecz K, Hess M. Comparing effects of natural betaine and betaine hydrochloride on gut physiology in broiler chickens. Poult Sci. 2022 Dec;101(12):102173. doi: 10.1016/j.psj.2022.102173. Epub 2022 Sep 9. PMID: 36228528; PMCID: PMC9573929.
[18] Commission Regulation (EU) No 432/2012 of 16 May 2012. Official Journal of the EU.
[19] Yde CC, Westerhuis JA, Bertram HC, Bach Knudsen KE. Application of NMR-based metabonomics suggests a relationship between betaine absorption and elevated creatine plasma concentrations in catheterised sows. British Journal of Nutrition. 2012;107(11):1603–15. doi:10.1017/S0007114511004909
[20] Atkinson W, Elmslie J, Lever M, Chambers ST, George PM. Dietary and supplementary betaine: acute effects on plasma betaine and homocysteine concentrations under standard and postmethionine load conditions in healthy male subjects. Am J Clin Nutr. 2008 Mar;87(3):577-85. doi: 10.1093/ajcn/87.3.577. PMID: 18326594.
[21] Cholewa JM, Guimarães-Ferreira L, Zanchi NE. Effects of betaine on performance and body composition: a review of recent findings and potential mechanisms. Amino Acids. 2014 Aug;46(8):1785-93. doi: 10.1007/s00726-014-1748-5. Epub 2014 Apr 24. PMID: 24760587.
[22] Lee EC, Maresh CM, Kraemer WJ, Yamamoto LM, Hatfield DL, Bailey BL, Armstrong LE, Volek JS, McDermott BP, Craig SA. Ergogenic effects of betaine supplementation on

strength and power performance. J Int Soc Sports Nutr. 2010 Jul 19;7:27. doi: 10.1186/1550-2783-7-27. PMID: 20642826; PMCID: PMC2915951.
[23] Hoffman JR, Ratamess NA, Kang J, Rashti SL, Faigenbaum AD. Effect of betaine supplementation on power performance and fatigue. J Int Soc Sports Nutr. 2009 Feb 27;6:7. doi: 10.1186/1550-2783-6-7. PMID: 19250531; PMCID: PMC2651845.
[24] Senesi P, Luzi L, Montesano A, Mazzocchi N, Terruzzi I. Betaine supplement enhances skeletal muscle differentiation in murine myoblasts via IGF-1 signaling activation. J Transl Med. 2013 Jul 19;11:174. doi: 10.1186/1479-5876-11-174. PMID: 23870626; PMCID: PMC3726349.
[25] Zawieja E, Machek S, Zanchi NE, Cholewa J, Woźniewicz M. Effects of chronic betaine supplementation on exercise performance: Systematic review and meta-analysis. J Sports Sci. 2024 Nov;42(22):2131-2144. doi: 10.1080/02640414.2024.2423578. Epub 2024 Nov 8. PMID: 39514262.
[26] Nobari H, Cholewa JM, Castillo-Rodríguez A, Kargarfard M, Pérez-Gómez J. Effects of chronic betaine supplementation on performance in professional young soccer players during a competitive season: a double blind, randomized, placebo-controlled trial. J Int Soc Sports Nutr. 2021 Oct 18;18(1):67. doi: 10.1186/s12970-021-00464-y. PMID: 34663363; PMCID: PMC8525016.
[27] Kültz D. Molecular and evolutionary basis of the cellular stress response. Annu Rev Physiol. 2005;67:225-57. doi: 10.1146/annurev.physiol.67.040403.103635. PMID: 15709958.
[28] Lever M, Slow S. The clinical significance of betaine, an osmolyte with a key role in methyl group metabolism. Clin Biochem. 2010 Jun;43(9):732-44. doi: 10.1016/j.clinbiochem.2010.03.009. Epub 2010 Mar 25. PMID: 20346934.
[29] Apicella JM, Lee EC, Bailey BL, Saenz C, Anderson JM, Craig SA, Kraemer WJ, Volek JS, Maresh CM. Betaine supplementation enhances anabolic endocrine and Akt signaling in response to acute bouts of exercise. Eur J Appl Physiol. 2013 Mar;113(3):793-802. doi: 10.1007/s00421-012-2492-8. Epub 2012 Sep 14. PMID: 22976217.
[30] Stoll B, Gerok W, Lang F, Häussinger D. Liver cell volume and protein synthesis. Biochem J. 1992 Oct 1;287 (Pt 1)(Pt 1):217-22. doi: 10.1042/bj2870217. PMID: 1329728; PMCID: PMC1133146.
[31] Cholewa JM, Wyszczelska-Rokiel M, Glowacki R, Jakubowski H, Matthews T, Wood R, Craig SA, Paolone V. Effects of betaine on body composition, performance, and homocysteine thiolactone. J Int Soc Sports Nutr. 2013 Aug 22;10(1):39. doi: 10.1186/1550-2783-10-39. PMID: 23967897; PMCID: PMC3844502.
[32] Pryor JL, Craig SA, Swensen T. Effect of betaine supplementation on cycling sprint performance. J Int Soc Sports Nutr. 2012 Apr 3;9(1):12. doi: 10.1186/1550-2783-9-12. PMID: 22471891; PMCID: PMC3353850.
[33] Soleimani E, Ardekani AM, Fayyazishishavan E, Farhangi MA. The interactive relationship of dietary choline and betaine with physical activity on circulating creatine kinase (CK), metabolic and glycemic markers, and anthropometric characteristics in physically active young individuals. BMC Endocr Disord. 2023 Jul 25;23(1):158. doi: 10.1186/s12902-023-01413-3. PMID: 37491240; PMCID: PMC10367233.
[34] Li C, Wang Y, Li L, Han Z, Mao S, Wang G. Betaine protects against heat exposure-induced oxidative stress and apoptosis in bovine mammary epithelial cells via regulation of ROS production. Cell Stress Chaperones. 2019 Mar;24(2):453-460. doi: 10.1007/s12192-019-00982-4. Epub 2019 Feb 25. PMID: 30805833; PMCID: PMC6439124.
[35] Armstrong LE, Casa DJ, Roti MW, Lee EC, Craig SA, Sutherland JW, Fiala KA, Maresh CM. Influence of betaine consumption on strenuous running and sprinting in a hot environment. J Strength Cond Res. 2008 May;22(3):851-60. doi: 10.1519/JSC.0b013e31816a6efb. PMID: 18438230.

[36] Trepanowski JF, Farney TM, McCarthy CG, Schilling BK, Craig SA, Bloomer RJ. The effects of chronic betaine supplementation on exercise performance, skeletal muscle oxygen saturation and associated biochemical parameters in resistance trained men. J Strength Cond Res. 2011 Dec;25(12):3461-71. doi: 10.1519/JSC.0b013e318217d48d. PMID: 22080324.
[37] Gao X, Zhang H, Guo XF, Li K, Li S, Li D. Effect of Betaine on Reducing Body Fat-A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2019 Oct 16;11(10):2480. doi: 10.3390/nu11102480. PMID: 31623137; PMCID: PMC6835719.
[38] Durkalec-Michalski K, Kusy K, Ciekot-Sołtysiak M, Zieliński J. The Effect of Beta-Alanine versus Alkaline Agent Supplementation Combined with Branched-Chain Amino Acids and Creatine Malate in Highly-Trained Sprinters and Endurance Athletes: A Randomized Double-Blind Crossover Study. Nutrients. 2019 Aug 21;11(9):1961. doi: 10.3390/nu11091961. PMID: 31438535; PMCID: PMC6769605.
[39] Xu J, Nie Z, Qiu X, Zhang J, Han S. Effects of betaine supplementation on inflammatory markers: a systematic review and meta-analysis of randomised controlled trials. Int J Food Sci Nutr. 2023 Nov;74(7):721-729. doi: 10.1080/09637486.2023.2257906. Epub 2023 Nov 15. PMID: 37733077.
[40] Zawieja E, Durkalec-Michalski K, Sadowski M, Główka N, Chmurzynska A. Betaine supplementation improves CrossFit performance and increases testosterone levels, but has no influence on Wingate power: randomized crossover trial. J Int Soc Sports Nutr. 2023 Dec;20(1):2231411. doi: 10.1080/15502783.2023.2231411. PMID: 37409757; PMCID: PMC10327519.
[41] Cholewa JM, Hudson A, Cicholski T, Cervenka A, Barreno K, Broom K, Barch M, Craig SAS. The effects of chronic betaine supplementation on body composition and performance in collegiate females: a double-blind, randomized, placebo controlled trial. J Int Soc Sports Nutr. 2018 Jul 31;15(1):37. doi: 10.1186/s12970-018-0243-x. PMID: 30064450; PMCID: PMC6069865.
[42] Alfthan G, Tapani K, Nissinen K, Saarela J, Aro A. The effect of low doses of betaine on plasma homocysteine in healthy volunteers. Br J Nutr. 2004 Oct;92(4):665-9. doi: 10.1079/bjn20041253. PMID: 15522136.
[43] McRae MP. Betaine supplementation decreases plasma homocysteine in healthy adult participants: a meta-analysis. J Chiropr Med. 2013 Mar;12(1):20-5. doi: 10.1016/j.jcm.2012.11.001. PMID: 23997720; PMCID: PMC3610948.
[44] Valayannopoulos V, Schiff M, Guffon N, Nadjar Y, García-Cazorla A, Martinez-Pardo Casanova M, Cano A, Couce ML, Dalmau J, Peña-Quintana L, Rigalleau V, Touati G, Aldamiz-Echevarria L, Cathebras P, Eyer D, Brunet D, Damaj L, Dobbelaere D, Gay C, Hiéronimus S, Levrat V, Maillot F. Betaine anhydrous in homocystinuria: results from the RoCH registry. Orphanet J Rare Dis. 2019 Mar 14;14(1):66. doi: 10.1186/s13023-019-1036-2. PMID: 30871635; PMCID: PMC6419445.
[45] European Medicines Agency. Cystadane 1 g betaine anhydrous – Summary of Product Characteristics. EMA; 2022 [cited 2025 Jun 16]. Available from: https://www.ema.europa.eu/en/documents/product-information/cystadane-epar-product-information_en.pdf
[46] Asma Ejaz, Laura Martinez-Guino, Allison B. Goldfine, Francesc Ribas-Aulinas, Valeria De Nigris, Sílvia Ribó, Alba Gonzalez-Franquesa, Pablo M. Garcia-Roves, Elizabeth Li, Jonathan M. Dreyfuss, Walt Gall, Jason K. Kim, Teodoro Bottiglieri, Francesc Villarroya, Robert E. Gerszten, Mary-Elizabeth Patti, Carles Lerin; Dietary Betaine Supplementation Increases Fgf21 Levels to Improve Glucose Homeostasis and Reduce Hepatic Lipid Accumulation in Mice. Diabetes 1 April 2016; 65 (4): 902–912. https://doi.org/10.2337/db15-1094

[47] Dantas, Matheus & Queiros, Victor & Silva, Tatiane & Silva, Alana & Fortes, Leonardo & Cholewa, Jason & Oliveira, Anna & Cabral, Breno. (2021). Acute effect of betaine supplementation on muscular endurance during resistance exercise in trained men: a pilot and randomized study. Journal of Trainology. 10. 25-29. 10.17338/trainology.10.2_25.
[48] EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), Turck D, Castenmiller J, De Henauw S, Hirsch-Ernst KI, Kearney J, Maciuk A, Mangelsdorf I, McArdle HJ, Naska A, Pelaez C, Pentieva K, Siani A, Thies F, Tsabouri S, Vinceti M, Cubadda F, Engel KH, Frenzel T, Heinonen M, Marchelli R, Neuhäuser-Berthold M, Pöting A, Poulsen M, Sanz Y, Schlatter JR, van Loveren H, Turla E and Knutsen HK, 2019. Scientific Opinion on the safety of betaine as a novel food pursuant to Regulation (EU) 2015/2283. EFSA Journal 2019;17(4):5658, 8 pp. https://doi.org/10.2903/j.efsa.2019.5658
[49] Schwab, U., Alfthan, G., Aro, A. et al. Long-term effect of betaine on risk factors associated with the metabolic syndrome in healthy subjects. Eur J Clin Nutr 65, 70–76 (2011). https://doi.org/10.1038/ejcn.2010.230
[50] Ashtary-Larky, D., Bagheri, R., Ghanavati, M., Asbaghi, O., Tinsley, G. M., Mombaini, D., … Wong, A. (2021). Effects of betaine supplementation on cardiovascular markers: A systematic review and Meta-analysis. Critical Reviews in Food Science and Nutrition, 62(23), 6516–6533. https://doi.org/10.1080/10408398.2021.1902938
[51] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle HJ, Naska A, Neuhäuser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Siani A, Sjödin A, Stern M, Tomé D, Vinceti M, Willatts P, Engel K-H, Marchelli R, Pöting A, Poulsen M, Schlatter JR, Turla E and van Loveren H, 2017. Scientific opinion on the safety of betaine as a novel food pursuant to Regulation (EC) No 258/97. EFSA Journal 2017;15(11):5057, 28 pp. https://doi.org/10.2903/j.efsa.2017.5057
[52] Ashtary-Larky D, Bagheri R, Tinsley GM, Asbaghi O, Salehpour S, Kashkooli S, Kooti W, Wong A. Betaine supplementation fails to improve body composition: a systematic review and meta-analysis. Br J Nutr. 2022 Sep 14;128(5):975-988. doi: 10.1017/S0007114521004062. Epub 2021 Oct 7. PMID: 34743773.
[53] Gao, X.; Zhang, H.; Guo, X.-f.; Li, K.; Li, S.; Li, D. Effect of Betaine on Reducing Body Fat—A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients 2019, 11, 2480. https://doi.org/10.3390/nu11102480