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Beta-hydroxy-beta-methylbutyrate in functional food ingredients: An overview of biosynthesis, metabolic mechanisms and applications

Xizi Zhang[1], Huijing Zhang[1], Jiaxing Li[1], Chenchen Qi[2], Di Zhang[3], Wei Chen[1], Chengtao Wang[1]**

[1]*Beijing Advanced Innovation Center for Food Nutrition and Human Health, Beijing Engineering and Technology Research Center of Food Additives, School of Food and Health, Beijing Technology and Business University, Beijing, P.R. China*

[2]*Xinjiang Xinkang Agricultural Development Co., Ltd, Urumqi, P.R. China*

[3]*School of Food and Biological Engineering, Jiangsu University, Zhenjiang, P.R. China*

**Corresponding authors: weichen@btbu.edu.cn; wctbtbu@163.com*

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Abstract: β-Hydroxy-β-methylbutyrate (HMB) is a metabolite of the essential amino acid leucine, which can be produced naturally in mammals and is also found in trace amounts in citrus fruits and fish. Studies have shown that HMB plays an important role in maintaining human health by improving muscle health and inhibiting muscle catabolism. This review summarises the synthesis and metabolism of HMB and discusses its potential use as a nutrient, highlighting and analysing the importance of HMB supplementation for athletes' physical recovery and the treatment of muscular dystrophy-related diseases between 2019 and 2025. This study will help us to deepen our understanding of the application of HMB as a dietary supplement for the treatment of different diseases, providing the latest insights into its sustainability.

Keywords: β-Hydroxy-β-methylbutyrate supplementation; dietary supplement; muscle; exercise; disease

In the current economic climate, maintaining muscle homeostasis is critical for overall health and quality of life, especially for the elderly and athletes (Huang et al. 2023). Inadequate protein intake fails to meet the body's daily requirements and leads to protein imbalance, thereby impairing muscle growth and function (Wu et al. 2024). There is growing evidence that protein, amino acid supplements, creatine and other nutrients can provide essential nutritional support (Owens 2018; Dolan et al. 2019).

β-Hydroxy-β-methylbutyrate (HMB), a metabolite of the amino acid leucine, is naturally produced in mammals. Its primary mechanism of action is to inhibit protein degradation and maintain muscle cell membrane integrity. Although foods such as citrus fruits and some fish contain trace amounts of HMB,

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their dietary content is so low that it is difficult to meet the body's needs through diet alone, so to improve bioavailability, they are often used as dietary supplements in the form of calcium β-hydroxy-β-methylbutyrate (HMB-Ca) (Ribeiro et al. 2024) and free acid HMB (HMB-FA) (Fuller et al. 2011).

Clinical and population studies have shown that HMB supplementation can increase body weight, muscle mass and strength, while reducing muscle damage in the elderly, cancer or AIDS patients, demonstrating promising potential in preventing and improving muscle loss (Holeček 2017). Therefore, this review summarises the multifaceted utilisation of HMB and the research progress for 2019–2025.

OVERVIEW OF HMB SYNTHESIS AND METABOLISM

The metabolic pathway of HMB, a metabolic by-product of leucine, has been comprehensively analysed in mammals (Garlick 2005). Figure 1A shows the production steps of HMB. Branched-chain amino acid aminotransferases initially catalyse most L-leucine metabolism to generate α-ketoisocaproic acid (α-KIC) in the liver (Zanchi et al. 2011). The acid is catalysed in the cytoplasm by KIC-dioxyenase to produce HMB. It is estimated that only about 2–10% of leucine is oxidised to HMB (Rathmacher et al. 2025). It is worth noting that the endogenous conversion of leucine to HMB is very limited, with healthy adults producing only 0.3–0.4 g of HMB per day (Zanchi et al. 2011). Foods such as avocado, cauliflower and citrus fruits contain HMB, but their content is extremely low, making obtaining large amounts of HMB directly from food difficult to achieve (Landi et al. 2019). Therefore, additional supplementation of HMB is very necessary.

Currently, HMB is produced commercially by chemical synthesis and microbiological production (Lee et al. 1997; Gao and Li 2021; Huang et al. 2024) (Figure 1B). Microbial production methods have received much attention due to the unpleasant odour and toxic peroxides produced as by-products of chemical synthesis. The strain commonly used for microbial fermentation of HMB is *Galactomyces reessii*, and the conversion of β-methylbutyric acid to HMB using *G. reessii* CBS179.60 was first reported in Japan in 1981. Subsequently, Lee et al. (1997) developed a two-step supplemental batch fermentation method using this strain, and obtained a HMB yield of 38 $g \cdot L^{-1}$ after 136 h. Other researchers used β-methylbutyric acid as a substrate and obtained a HMB yield of 29.0 $g \cdot L^{-1}$ after 108 h. Despite the advances in microbial fermentation, it is costly and complex to produce. For example, a crucial limitation for optimising the biotransformation of HMB is α-ketoisocaproate dioxygenase (Gao and Li 2021). It has the same catalytic activity as 4-hydroxyphenylpyruvate dioxygenase from rat liver. 4-Hydroxyphenylpyruvate dioxygenase is also present in fungi and plants, but with different substrates and a different catalytic mechanism. At the same time, leucine is economically challenging to use as a starting substrate, so it is particularly important to explore alternative enzymes with the same function and cost-effective substrates.

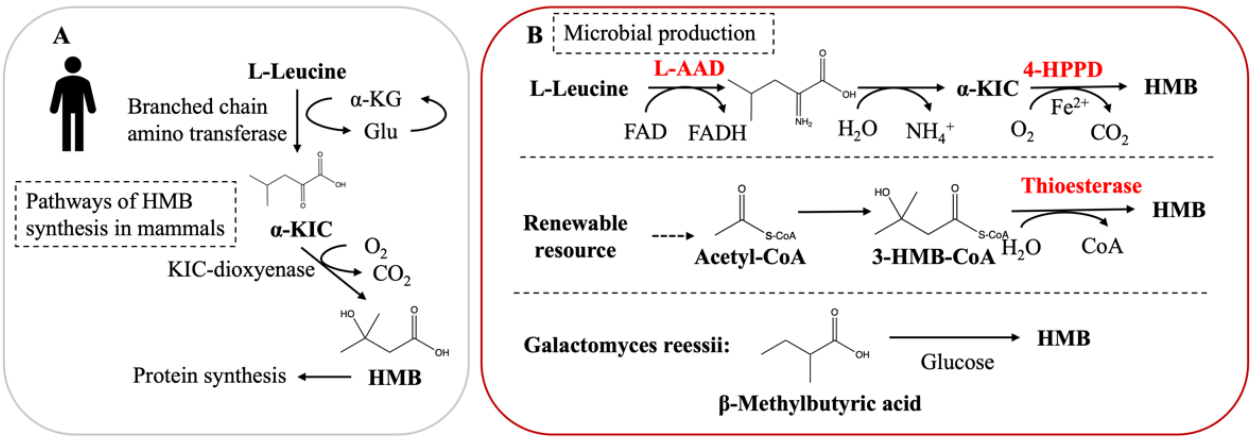

Figure 1. The synthesis pathway of β-hydroxy-β-methylbutyrate (HMB): (A) biosynthesis of HMB in mammals, (B) using chemical and microbial synthesis to produce HMB

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THE SAFETY OF HMB

The absence of adverse effects from HMB in recent toxicological and clinical investigations supports its safety and suitability as a dietary supplement (Nissen et al. 2000). A bacterial reverse mutation assay, an *in vitro* mammalian chromosome aberration assay, and a mammalian erythrocyte micronucleus test were conducted by the Food Research Laboratory of Japan and the results were negative (Baxter et al. 2005; Fuller et al. 2014; Pitchford et al. 2018) performed oral toxicity experiments using SD rats: Sprague-Dawley rats and no adverse effects were observed in all dose groups, showing that HMB has a high safety profile. Kreider et al. (1999) supplemented subjects at different HMB doses with no significant effects on 31 metabolic and haematological indices at 28 days of clinical chemistry analysis. The results of Gallagher et al. (2000) and Baier et al. (2009) also showed that HMB supplementation does not adversely affect the body's liver function, lipids and immune system.

In 1995, HMB passed the US Food and Drug Administration's Generally Recognized as Safe (GRAS) assessment and was approved for use in medical nutritional foods and conventional foods. In 2005, CaHMB was also recognised as a GRAS substance with a recommended intake of 3 g·day^{-1} (Zhang et al. 2024b), and the US Food and Drug Administration increased the use level to 6 g·day^{-1} in 2009 (Szczesniak et al. 2015). Gradually, many countries are using it as a dietary supplement (Figure 2), for example, the European Union and Japan included HMB as a food ingredient in 1997 and 2009, respectively; in China, the Ministry of Health approved the use of HMB in sports nutrition food in 2011, and expanded its use to beverages, dairy products, cocoa products, and confectionery in 2017 (Zhang et al. 2024a). This showed that HMB is recognised as safe. However, further studies are still needed to determine optimal dosage and potential combined effects (Wilson et al. 2008).

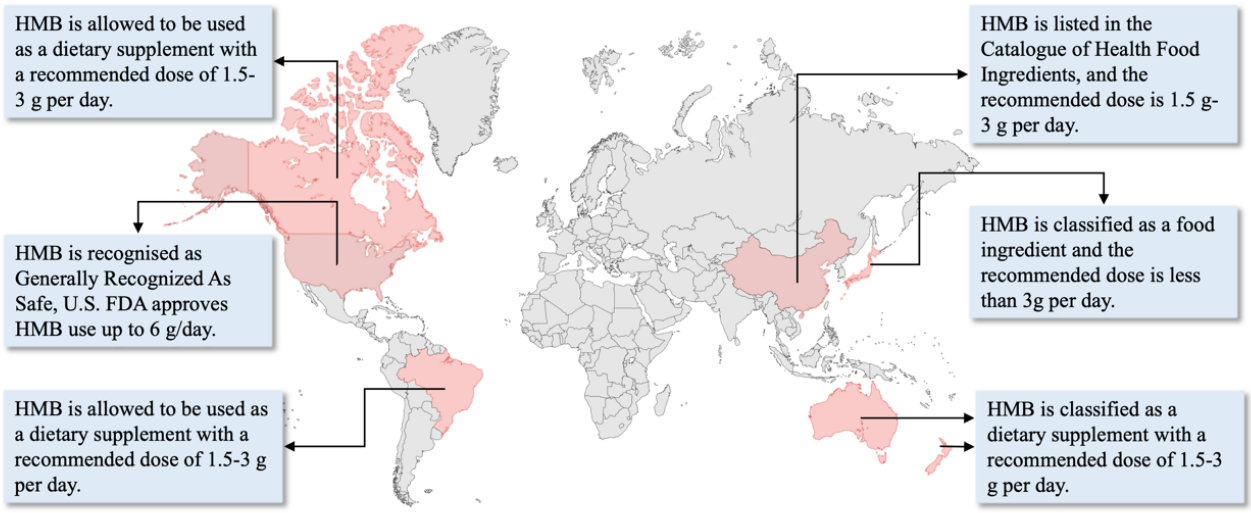

Figure 2. Standards for β-hydroxy-β-methylbutyrate (HMB) use in different countries

APPLICATION OF HMB IN FOOD

Since its approval for use as a general food ingredient in the European Union in 1997, HMB has gradually been incorporated into products available on the international market (Palisin and Stacy 2005) (Figure 3). HMB can be used synergistically with a variety of proteins (Jäger et al. 2017) (including whey protein concentrate, milk protein concentrate, whey isolate and other dairy proteins, as well as various types of plant proteins), and it can also be compounded with vitamins, minerals and other nutrient-fortified formulas, thereby enhancing the functional value of a product.

However, there are challenges to the development of the product. Optimising the production process to reduce costs continues to be a critical issue (Palisin and Stacy 2005), as well as differences in the health management of HMB in different countries, and consumer awareness needs to be further improved. In the future, with the development of nutrition and other technologies, HMB-related food products will become more targeted, accessible, and widely adopted.

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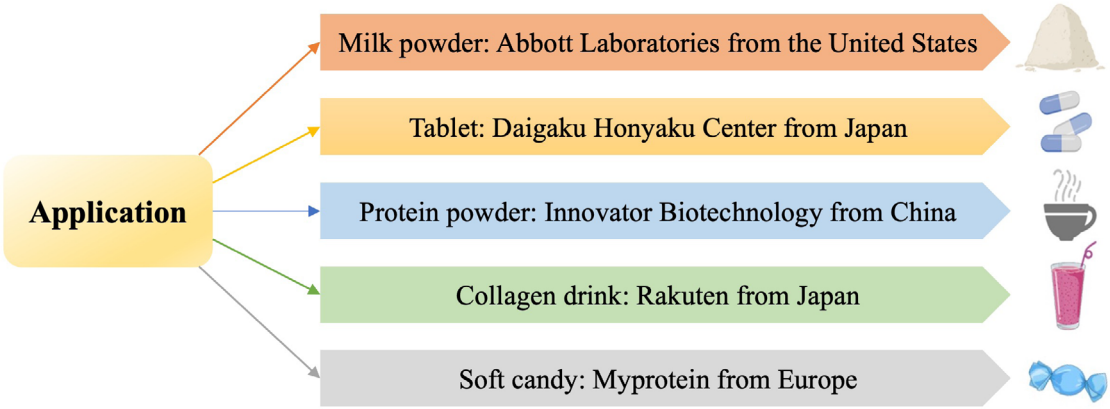

Figure 3. The application of β-hydroxy-β-methylbutyrate (HMB) in foods

THE ROLE OF HMB IN EXERCISE

Exercise-induced muscle damage, muscle atrophy, and sarcopenia are only a few conditions that may benefit from HMB supplementation. Resistance training is a training modality that increases muscle strength and explosive power (Gao and Li 2021). Similarly, high-intensity resistance training promotes protein synthesis, muscle cell signaling flux, and hormonal response. Amino acid intake, alone or combined with resistance training, improves strength performance after training (Vukovich et al. 2001). Evidence suggests resistance and high-intensity exercises combined with HMB intake improve hormone levels and increase muscle mass, strength, and performance. This effect may be achieved through several HMB-mediated mechanisms (Figure 4): (*i*) suppression of proteolysis by inhibition of the ubiquitin-proteasome systém (Eley et al. 2008), (*ii*) promotion of β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) overexpression (Hagve et al. 2024), It should be noted that HMG-CoA serves as a precursor in cholesterol biosynthesis. Pathologically elevated cholesterol levels are risk factors for atherosclerosis and coronary heart disease (Marcoff and Thompson 2007). Importantly, research indicates that statins, a class of drugs that function as HMG-CoA reductase inhibitors, can reduce cholesterol levels without interfering with the generation of leucine and HMB (Hagve et al. 2024), (*iii*) enhancement of protein synthesis via the mammalian target of rapamycin (mTOR)/p70 ribosomal protein S6 kinase (p70S6K) and serine/threonine protein kinase AKT pathway (Wilkinson et al. 2013; Eley et al. 2007), and (*iv*) elevation of satellite cell proliferation (Alway et al. 2013). We will provide a brief overview of studies that have explored the effects of ingesting HMB or HMB-containing supplements on training populations.

Body composition and cellular health are usually analysed in sports training using bioelectrical phase angle (PhA) measurements and bioimpedance vector analysis (BIVA) patterns to optimise athletic performance. Campa et al. (2021) assessed the effects of HMB supplementation on body composition during an 8-week training period, and they found that the metabolite of leucine (HMB-Ca and HMB-FA) had no significant effect on PhA, BIVA patterns, or strength performance. Similarly, Tritto et al. (2019) reported no additional benefit of HMB supplementation for body composition improvement by assessing muscle strength (1RM: One Repetition Maximum bench press and squat tests) and muscle hypertrophy (ultrasound measurement of muscle thickness). There are additional studies demonstrating that HMB supplementation combined with resistance training in healthy men does not improve muscle growth and strength (Teixeira et al. 2019a,b). Fairfield et al. (2022) were the first to evaluate the effects of exercise and HMB on middle-aged women, and their results showed that HMB had no significant effect on overall body composition. Similarly, Mendes et al. (2024) found no additional effect of HMB supplementation in older women; however, Osuka et al. (2021) subsequently reported that combining exercise training with HMB supplementation improved muscle mass in this population. A systematic review and meta-analysis by Jakubowski et al. (2020), which evaluated the efficacy of HMB in enhancing fat-free mass (FFM) and strength gains during resistance

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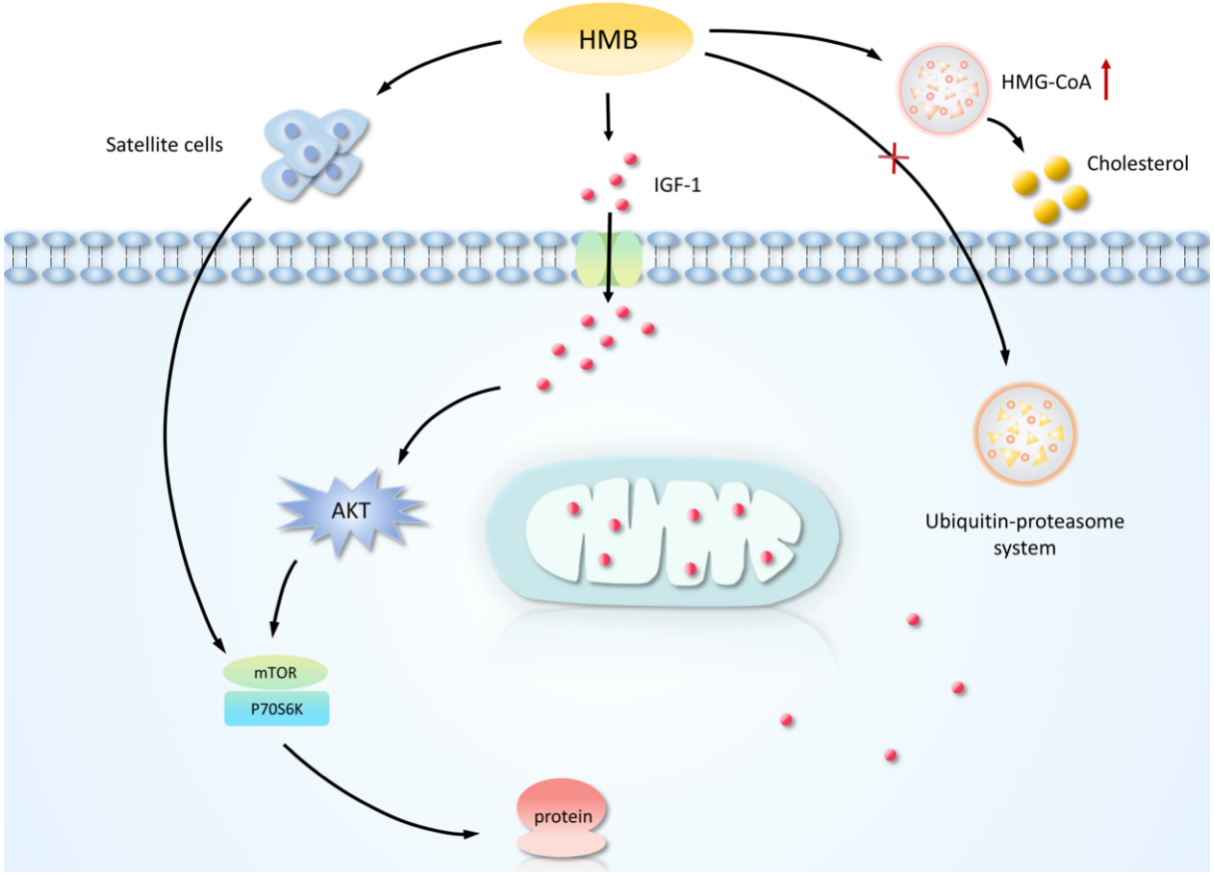

Figure 4. Effects of β-hydroxy-β-methylbutyrate (HMB) supplementation on the organism and possible signalling pathways that promote protein synthesis.

training in young adults, found a significant effect only on total body weight, with no notable impact on FFM, fat mass (FM), or strength outcomes.

However, a portion of the research demonstrated different results than those described above especially in competitive athletes. In a 4-week study, supplementation with 3 g of HMB per day protected lean body mass during acute weight loss (a 5% reduction in body weight) in collegiate boxers and reduced muscle strength loss, muscle damage and catabolic stress (Chang et al. 2023). Fernandez-Landa et al. (2020) showed that combined supplementation with HMB and creatine showed significant improvements in anaerobic capacity in elite male endurance athletes, particularly during short-duration, high-intensity exercise. Likewise, Kaczka et al. (2021) reported that co-supplementation with HMB and L-arginine α-ketoglutarate can help young track and field athletes maintain better athletic performance during high-intensity training. When combined with other nutrients, HMB maximises the limiting nutrients required for athletic performance. Stahn et al. (2020) performed 12 weeks of resistance training on 12 healthy men, and found that combined supplementation with protein and HMB led to an increase in FFM segmentation compared to protein supplementation alone. In a one-year study, supplementation of older adults with HMB-Ca and vitamin D3 enhanced muscle function and strength in older adults (Rathmacher et al. 2020). According to a systematic evaluation and meta-analysis (Shakibaee et al. 2023), HMB supplementation (3 g HMB per day for 7 weeks) provided greater changes in hormone concentrations (testosterone, cortisol, and insulin-like growth factor). Increases in the concentrations of these hormones are important variables in improving physical performance (Arazi et al. 2013).

Although research data on HMB is somewhat divergent, a synthesis of the available evidence suggests that HMB may positively impact exercise performance and muscle health in a number of ways. Specifically, HMB has shown the potential to modulate muscle protein metabolism, promote muscle mass growth, enhance aerobic capacity, and mitigate exercise-induced muscle damage.

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THE ROLE OF HMB IN DISEASE

Past research mainly focused on disclosing the causes of muscle mass and strength loss and finding appropriate solutions for them (Jakubowski et al. 2020). Few therapeutic options are available for conditions caused by muscle wasting or prolonged inactivity, and even the most effective agents that enhance muscle strength show limited efficacy and are associated with adverse effects (Fernandez-Landa et al. 2020). HMB has been shown to treat sarcopenia and muscle atrophy, improving muscle strength and hormone levels. For instance, Espina et al. (2022a) reported that HMB supplementation improved muscle performance and helped protect patients with liver cirrhosis from sarcopenia. When combined with other dietary supplements, HMB further promotes protein synthesis, as discussed previously. It also plays an important role during cardiac surgery by reducing the risk of systemic inflammatory responses and lowering morbidity and mortality (Aquilani et al. 2017). Furthermore, in patients with pancreatic cancer, HMB relieves sarcopenic obesity and cachexia (Kim et al. 2013). Some studies imply that supplements such as HMB do not increase fat mass but improve overall health (Duan et al. 2019). The following section summarises recent progress in understanding the role of HMB in specific diseases (Figure 5).

Sarcopenia. Skeletal muscles account for approximately 40% of the body weight of a healthy human and have a vital role in metabolism (Sanz-Paris et al. 2018). Sarcopenia is a syndrome caused by decreased skeletal muscle mass and slow anabolism. It mainly occurs in the older population, where 20% are over 70-year-olds, and up to 50% are over 80-year-olds (Weihrauch and Handschin 2018), increasing the risk of falls and hip fractures. Current treatment strategies for sarcopenia include drug therapy, exercise, and nutritional interventions. However, drug therapy remains limited in effectiveness (Tepaske et al. 2001), and combined exercise and nutrition are the preferred approaches in clinical practice.

Table 1 summarises randomised controlled trials (RCTs) assessing the effects of combined HMB and exercise interventions on body composition (lean body mass, fat mass and their proportions) and physical function (step speed, grip strength), excluding subjective bias in study design and population selection. However, differences in population characteristics and study design may still affect the results. Existing studies cover a wide range of populations of different ages, genders and training status.

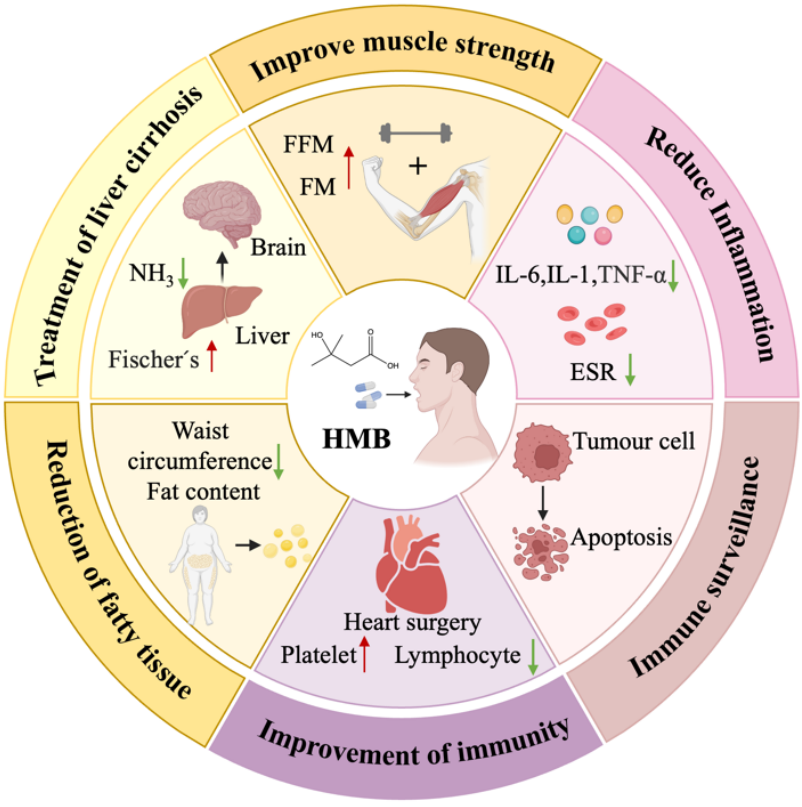

Figure 5. The role β-hydroxy-β-methylbutyrate (HMB) plays in specific disease types

ESR – erythrocyte sedimentation rate; FFM – fat-free mass; FM – fat mass

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Table 1. A randomised controlled study of the use of β-hydroxy-β-methylbutyrate (HMB) in the treatment of sarcopenia

Country	Sample size	Age	Intervention	Control	Duration	Over measures	Result	Reference
China	200	M: 76.3 W: 79.1	RT + HMB (3 g·day^{-1}) RT HMB (3 g·day^{-1})	placebo	3 months	DXA, GS, BI, HHS, VAS	RT+HMB/ RT:FM/GS ($P < 0.05$) HMB: NS	Han et al. (2022)
China	34	≥ 60	HMB (3 g·day^{-1})	placebo	12 weeks	GS, gait speed, blood, BIA	GS : $P < 0.001$ Gait speed: $P = 0.014$ FFM: $P = 0.001$ TWEAK: $P = 0.041$	Yang et al. (2023)
Italy	22	59.96.2	HMB (3 g·day^{-1})	juice	12 weeks	ASMI, FFMI, FMI, HG	ASMI: $P = 0.0003$ HG: $P = 0.001$	Lattanzi et al. (2019)
Spain	32	81.6 ± 9.3	HMB (3 g·day^{-1}) RT	maltodex- trin	12 weeks	HG, gait speed, SPPB, BIA	HG: $P = 0.042$ SPPB: $P < 0.05$ FFM: NS	Meza- Valderrama et al. (2024)
Japan	156	W: 65–79	HMB (1.5 g·day^{-1}) RT	maltodex- trin	12 weeks	BIA, HG, blood	NS	Osuka et al. (2021)
Singapore	36	71.5	HP ONS (660 mL·day^{-1}) HMB (3 g·day^{-1}) RT	placebo	2–4 weeks	IMAT, 6MWD, gait speed	IMAT: $P = 0.028$ Gaid speed: $P = 0.01$	Koh et al. (2024)
China	112	18–80	HMB (3 g·day^{-1}) RT	placebo	2 weeks	6WMD, SPPB, MRC score, GS	6WMD: $P < 0.01$ MRC/GS: $P < 0.05$	Wu et al. (2023)

M – men; W – woman; RT – resistance training; DXA – dual-energy x-ray absorptiometry; GS – grip strength; BI – barthel index; HHS – harris hip score; VAS – visual analog scale score; FFM – fat-free mass; FM – fat mass; NS – no significant effect(s); BIA – bioelectrical impedance analysis; ASMI – Appendicular Skeletal Muscle Mass Index; SPPB – Short Physical Performance Battery; HG – handgrip strength; HP ONS – high-protein oral nutritional supplements; IMAT – intramuscular adipose tissue; 6WMD – six minutes walking distance ; MRC – Medical Research Council; FFMI – Fat-Free Mass Index; FMI – Fat Mass Index; TWEAK – Tumour necrosis factor-like weak inducer of apoptosis

Long-term supplementation of HMB combined with resistance training in older adults has been shown to significantly improve fat mass and grip strength (Han et al. 2022). However, in older women with low muscle mass, HMB produced only minimal improvements in physical performance (Osuka et al. 2021) Moreover, short-term supplementation in acutely injured older adults did not alleviate muscle damage (Han et al. 2022). A recent meta-analysis found no significant benefits of HMB plus exercise on body composition in patients with sarcopenia compared to placebo combined with exercise interventions. Nevertheless, one study reported that HMB supplementation, due to its anti-catabolic properties, positively influenced body composition in bedridden or sedentary older adults (Costa Riela et al. 2021). In addition, the prevalence of sarcopenia is strongly associated with fat-free adipose tissue (FFAT). FFAT needs to be taken into account when using dual-energy x-ray absorptiometry (DXA) to measure lean body mass in the extremities, as uncorrected FFAT data from DXA may lead to an underestimation of the actual prevalence of sarcopenia (Loenneke et al. 2016; Abe et al. 2019).

In summary, current evidence suggests that combining exercise with HMB supplementation may enhance physical function in patients with muscle wasting disorders. However, its effects on outcomes such as muscle mass, muscle strength, and body composition appear limited. Importantly, most studies have notable limitations, including small sample sizes, variable designs, and inconsistent results. Thus, large-scale, multicentre,

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high-quality randomised controlled trials with systematic meta-analyses are urgently needed to clarify its clinical efficacy.

Skeleton muscular diseases. Patellar tendinopathy (PT) is one of the most common skeletal pain disorders in sports, with up to a 50% prevalence in athletes who require repetitive jumping movements (Supinski et al. 2021). PT is characterised by vascular hyperplasia, collagen abnormalities, increased infiltration of inflammatory cells, and protein deficiency (Viana et al. 2021). Strength-training exercises and stretching are the cornerstone of rehabilitation for PT. Squats, for example, are widely used to improve muscle coordination and strength (Nakamura et al. 2020). Nutritional supplementation may further support rehabilitation from sports-related injuries. However, evidence on its effectiveness in musculoskeletal disorders remains limited (Lian et al. 2005).

In a recent study, eight athletes with PT followed a four-week rehabilitation program combining eccentric training, stretching, and 3 g·day^{-1} of HMB. Supplementation improved muscle performance in these athletes (Sanchez-Gomez et al. 2022). Conversely, another trial tested a combination of arginine, glutamine, and HMB for treating pressure sores in patients with hip fractures and found no therapeutic benefit (Miu et al. 2021). Notably, 66% of patients with hip fractures develop pressure sores, and prolonged bed rest reduces mitochondrial capacity. Under such conditions, HMB supplementation may provide little or no benefit (Standley et al. 2020).

Although recent data indicate that HMB optimises the effectiveness of treating some skeletomuscular conditions, it has a minor role in the treatment. Whether HMB and other nutritional supplements combined with moderate training can improve their clinical effect remains an open question.

Cardiac disease. During cardiac surgery, patients often experience hypothermia and inflammatory responses triggered by excessive free radical production. Malnutrition is common in individuals with cardiac disease, particularly in those with sarcopenia, cachexia, or systemic inflammation. Anti-inflammatory nutrients and amino acid based supplements may help regulate elevated levels of inflammatory mediators in these patients (Aquilani et al. 2017).

Based on that, it makes clinical sense for patients to take nutrients prior to cardiac surgery. The metabolite of leucine, HMB, may have a role in reducing the inflammatory response. Evidence suggests HMB reduces the inflammatory response before a cardiac surgical procedure. Its mechanism of action is likely associated with the inhibition of a key inflammatory pathway: surgical trauma can trigger an inflammatory response, during which tumour necrosis factor-alpha (TNF-α) activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thereby initiating the expression of various pro-inflammatory factors, such as IL-1β and IL-6. Research indicates that HMB suppresses TNF-α-induced IL-6 production by inhibiting the activation of NF-κB, without affecting cell proliferation (Miyake et al. 2019). Norouzi et al. (2022) studied the effectiveness of glutamine, HMB, and arginine supplementation in patients undergoing cardiac operation. A supplementation regimen consisting of 7 g L-arginine, 7 g L-glutamine, and 1.5 g HMB or placebo was given to 60 patients daily for 1 month before the operation. Preoperative examination revealed the co-supplementation significantly improved select haematological parameters and reduced inflammatory factors. Hence, taking nutritional supplements before cardiac surgical procedures seems a reasonable clinical option for patients with cardiac diseases.

Although preoperative combined nutritional supplementation generally benefits patients, its effects are individualised. Therefore, preoperative nutritional risk should be assessed, and interventions should be tailored accordingly. In addition, Norouzi et al. (2022) did not use supplementation with one compound as a control, so they could not determine which nutrient played the central role in mitigating the immune response. In summary, future studies should focus on individualising treatment and clarifying the contribution of each nutrient.

Liver cirrhosis. One of the main features of liver cirrhosis is malnutrition, characterised by increased fatty acid oxidation. This reduces glucose utilisation and protein synthesis, leading to sarcopenia and muscle mass loss (Periyalwar and Dasarathy 2012). Some experts recommend that patients with liver cirrhosis take combined leucine, isoleucine, and valine branched-chain amino acids at a 2 : 1 : 1 ratio. Leucine, for example, stimulates the oxidation of other branched-chain amino acids, enhancing the effect of muscle protein imbalance. Its natural metabolite, HMB, further promotes protein synthesis via the mTOR pathway (Giron et al. 2016). In patients with severe cirrhosis following liver transplantation, sarcopenia often does not improve. Its severity is decisive for the length of stay in the intensive care unit and the duration of hospitalisation (Montano-Loza et al. 2014). Therefore, mitigating sarcopenia associated with liver cirrhosis and liver transplantation is crucial.

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Recent studies have investigated the effects of HMB supplementation on body composition in patients with cirrhosis and liver transplantation (Table 2). Researchers found that HMB-containing Oral nutritional supplements (ONS) increased Fischer's ratio in cirrhosis and malnutrition without altering plasma Gln or ammonia levels (Espina et al. 2021). In a subsequent study, patients received ONS for 12 weeks; while fat-free mass remained unchanged in both groups, grip strength increased by 13% in the HMB group, with a downward trend in minimal hepatic encephalopathy (Espina et al. 2022b). However, recent research has shown that HMB supplementation does not significantly affect muscle mass, function, or quality of life in liver transplant patients (Ferreira et al. 2023).

In conclusion, HMB may serve as a prophylactic intervention for cirrhosis and liver transplant patients over a 12-week ONS period, but clinical evidence is limited, and further studies are needed to confirm these findings.

Obesity. Obesity, which increases the risk of insulin resistance and diabetes, represents a major public health challenge. Research indicates that HMB may promote weight loss and improve fat distribution (Zheng et al. 2021a). Although this intervention shows promise for reducing body fat, most studies on this topic have been conducted in animal models. For instance, experiments using physiologically relevant pig models have demonstrated that HMB supplementation prevents fat accumulation by inhibiting lipogenesis and enhancing lipid metabolism (Zheng et al. 2021b). Similarly, HMB administration has been shown to prevent obesity in mice (Duan et al. 2019). A key player in this process is the mitochondrion (Heinonen et al. 2015), with substantial evidence linking impaired mitochondrial respiration to obesity. Supporting this, a human study reported reduced mitochondrial aerobic capacity in obese individuals (Yin et al. 2014). Furthermore, treatment of C2C12 myotubes with either leucine or HMB significantly increased mitochondrial mass and respiratory capacity (Zhong et al. 2019). Thus, mitochondrial respiration may be a critical regulator of lipid metabolism and a promising future therapeutic target for combating obesity.

Cancer cachexia. Pancreatic cancer is often associated with sarcopenic obesity and cachexia, and effective treatment options are limited. HMB supplementation may offer a cost-effective approach, as it promotes cancer immunosurveillance and protects skeletal muscle. Coleman et al. (2021) performed experiments on mice and found that HMB exhibits musculoprotective activity and antitumor effects against pancreatic cancer in the context of obesity. However, the exact

Table 2. A randomised controlled study of the use of β-hydroxy-β-methylbutyrate (HMB) in the treatment of liver cirrhosis

Country	Sample size	Intervention	Control	Duration	Over measures	Result	Reference
Spain	34	ONS: 1.5 g HMB twice a day	HP ONS	12 weeks	BIA, GGT, AST, ALT, HG, MELD	FFM: NS FM: $P < 0.05$ HMB group: HG increased by 13%	Espina et al. (2022b)
Spain	43	ONS: 1.5 g HMB twice a day	HP ONS	12 weeks	PHES, Fischer's ratio, BCAA	HMB group: BCAA: $P < 0.05$ Fischer's ratio: $P < 0.05$	Espina et al. (2021)
Italy	22	HMB (3 g·day^{-1}) twice a day	juice	12 weeks	DEXA, 6MWT, HG, MAMC	ASMI: $P < 0.05$ MAMC: $P < 0.05$ HG: $P < 0.01$	Lattanzi et al. (2019)
Brazil	47	HMB (3 g·day^{-1})	maltodextrin	12 weeks	MAMC, FI	NS	Ferreira et al. (2023)

ONS – oral nutritional supplements; HP ONS – high-protein oral nutritional supplements; BIA – bioelectrical impedance analysis; HG – handgrip strength; GGT – gamma-glutamyl transpeptidase; AST – aspartate transaminase; ALT – alanine transaminase; MELD – Model for End-stage Liver Disease, PHES – hepatic encephalopathy score; BCAA – branched chain amino acids; MAMC – mid-arm muscle-circumference, ASMI – Appendicular Skeletal Muscle Mass Index; 6WMD – six minutes walking distance; FFM – fat-free mass; FM – fat mass; NS – no significant effect(s); DEXA – Dual-Energy X-ray Absorptiometry; FI – Frailty index

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mechanism remains unclear, requiring further exploration combined with clinical experiments.

Malnutrition and complications cause death in roughly 20% of cancer patients, further exacerbated by increasing treatment toxicity and drug resistance. Timely nutritional supplementation is therefore essential. Cornejo-Pareja et al. (2021) studied the effects of high-calorie, high-protein supplementation containing HMB on nutritional status, body weight, and muscle-related parameters. The study included 283 patients with malnutrition, of which 63% had cancer. Participants showed increased body weight, fat mass, and grip strength after 6 months of oral supplementation. In patients at nutritional risk after bladder cancer surgery, HMB-containing ONS maintained weight and reduced the probability of complications (Ritch et al. 2019), Similarly, patients with resected retroperitoneal soft tissue sarcomas showed the same results in postoperative recovery (Previtali et al. 2020). Although research is limited, these studies suggest that HMB supplementation may improve postoperative physical conditions.

While studies indicate that HMB supplementation could be beneficial in managing cancer cachexia, its underlying mechanisms remain largely unknown. Therefore, future research should focus on specific populations, randomized controlled trials, and scheduled follow-ups.

CONCLUSION

HMB is well-known for its muscle-protective properties and has been approved for use in health foods and specialised medical products in many countries. Future efforts should focus on green and sustainable production processes, particularly through biosynthetic technology and metabolic engineering to optimise HMB metabolic pathways and increase yield. The market application of HMB should also be increased by further developing HMB nutritional supplements for special populations (such as elderly people, athletes and patients with chronic diseases).

Additionally, it is important to note that therapies to increase muscle strength and slow down protein breakdown should not rely solely on HMB supplementation. Combining HMB with resistance training or other dietary supplements may achieve superior outcomes. Since many patients have malnutrition due to diseases, an untimely treatment may cause sarcopenia and muscle atrophy. Hence, long-term supplementation with HMB or HMB-containing supplements might improve muscle mass and alleviate sarcopenia in patients. In critically ill patients, systemic protein catabolism increases dramatically, emphasising the need for effective treatment strategies. Progress in treating these patients with supplements requires a thorough understanding of the mechanism that accelerates proteolysis and depletes endogenous branched-chain amino acids (Ten Have et al. 2022). Patients with obesity are at higher risk of insulin resistance and diabetes (Rios-Hoyo and Gutierrez-Salmean 2016). Although branched-chain amino acid levels rise in these patients, their relationship with obesity and insulin resistance remains unclear. Therefore, longer-term and detailed studies are necessary to clarify the mechanism of action of HMB action and optimise its efficacy.

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