γ-Aminobutyric acid found in fermented foods and beverages: current trends

Novia R.M. Sahaba, Edy Subrotoa, Roostita L. Baliab, Gemilang L. Umaa,a,c,*

a Magister of Agro-Industrial Technology, Faculty of Agro-Industrial Technology, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang Km.21 Jatinangor 45363, Indonesia
b Faculty of Animal Husbandry, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang Km.21 Jatinangor 45363, Indonesia
c Center for Environment and Sustainability Science, Universitas Padjadjaran, Jl. Sekeloa Selatan No. 1 Bandung 40134, Indonesia

ARTICLE INFO
Keywords:
Food science
Microbiology
Natural product chemistry
Nutrition
Materials science
Fermented foods and beverages
Functional effect
GABA
GAD
L-glutamic acid

ABSTRACT
γ-aminobutyric acid (GABA) is synthesised by glutamic acid decarboxylase which catalyses the decarboxylation of L-glutamic acid. L-glutamic acid is formed by α-ketoglutarate in the TCA cycle by glutamic acid dehydrogenase (GDH). GABA is found in the human brain, plants, animals and microorganisms. GABA functions as an antidepressant, antihypertensive, antidiabetic and immune system enhancer and has a good effect on neural disease. As GABA have pharmaceutical properties, conditions for GABA production need to be established. Microbiological GABA production is more safe and eco-friendly rather than chemical methods. Moreover, it is easier to control conditions of production using microorganisms compared to production in plants and animals. GABA production in fermented foods and beverages has the potential to be optimised to increase the functional effect of fermented foods and beverages.

1. Introduction

The synthesis of γ-aminobutyric acid (GABA), a non-protein amino acid with four carbon atoms, is catalysed by the enzyme glutamic acid decarboxylase (GAD) and the cofactor pyridoxal-5-phosphate (PLP) from L-glutamate [1, 2, 3]. GABA has been isolated from many sources, such as tea leaves, mulberry leaves, tomato, animals, lactic acid bacteria (LAB), yeasts and moulds [1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. GABA is also found in fermented foods and beverages such as tempe/fermented soybean, dadih/fermented buffalo milk, asam durian/fermented durian, tape singkong/fermented cassava, ikan budu/fermented fish, sake, yogurt-sake, sourdough, mulberry beer, kimchi and zlatar cheese [9, 11, 16, 19, 20, 21, 22, 23].

γ-aminobutyric acid has potential health benefits such as antidepressant, sedative, antihypertensive, antidiabetic, anticarcinogenic and immune system enhancer [14, 24, 25, 26, 27, 28, 29]. In microorganisms, GABA is involved in spore germination and causes acid resistance in bacteria [30]. In animals, GABA performs essential activities as an inhibitory neurotransmitter on several routes, namely the central nervous system and peripheral tissue. GABA also has a good effect on patients with Huntington, Parkinson’s, Alzheimer’s, stiff-person syndrome and schizophrenia [3].

γ-aminobutyric acid production using plants and animals is not easy. GABA concentration is low in plants and the production mechanism is unclear [31]. In contrast, GABA production using microorganisms has been studied extensively. The factors which influence GABA production are easily controlled, so that researchers mostly focused on GABA production using microorganisms [3]. Moreover, GABA production using microorganisms is safe and eco-friendly compared to chemical methods [3, 31, 32].

Microorganisms are found everywhere; however, they are mainly isolated from fermented foods and beverages. Fermentation involves bacteria, yeasts and moulds, which produce GABA. Microorganism-based GABA production in fermented food has immense prospects [32]. The availability of nutrients in food, along with microorganisms, allows the natural synthesis of GABA. All it needs to do is optimize the fermentation process in fermented foods to maximize the GABA content.

γ-aminobutyric acid was first discovered in plants in 1949 by Steward [33]. The earliest finding was in the form of alpha butyric acid in potatoes [34]. There is 79122 research papers and 18047 article reviews with numerous topics relating to GABA, such as its existence in plants, animals, microorganisms, fermented food and beverages, extraction and
purification, as well as numerous clinical trials of GABA against diseases. The main focus of this article is the existence of GABA in fermented foods and beverages which is contributed by microorganisms.

2. γ-aminobutyric acid metabolic pathway

In microorganisms, glucose metabolism produces several metabolites; one of which is GABA. Glucose is converted to pyruvate during glycolysis. Thereafter, pyruvate is converted to acetyl-CoA, which reacts with oxaloacetate and enters the TCA cycle forming citrate. Citrate is converted to isocitrate and α-ketoglutarate, which can be converted to GABA by several microorganisms via glutamic acid dehydrogenase (GDH) and GAD, as shown in Figure 1 [33].

The formation of GABA by the TCA cycle via glutamate is called the GABA shunt [33]. The α-ketoglutarate from the TCA cycle is converted to glutamate by GDH and then converted to GABA by decarboxylation. The reaction is irreversible, catalysed by GAD and needs pyridoxal phosphate (PLP) as a cofactor [2, 33, 34, 35].

The GABA shunt may degrade GABA by γ-aminobutyric acid aminotransferase (GABA-AT) and semialdehyde dehydrogenase (SSADH). These enzymes convert GABA to succinic semialdehyde (SSA) and the second reaction converts SSA to succinate by SSADH [33]. The TCA cycle occurs in the mitochondria whereas the formation of GABA from glutamate occurs in the cytosol, as GABA is transformed by GABA-AT and SSADH, it goes back to the mitochondria [36].

3. Microorganisms roles in γ-aminobutyric acid production

γ-aminobutyric acid synthesis of L-glutamate in metabolism is catalyzed by the GAD enzyme. As shown in Table 1, GAD can be produced by many microorganism like LAB, yeasts and fungi [15, 32, 37, 38, 39, 40, 41].

LAB, such as Streptococcus thermophilus, Lactobacillus brevis, L. paracasei, L. ftsii, L. plantarum and Bifidobacterium adolescentis, have GAD enzyme activity and are widely used for GABA production. These bacteria are commonly isolated from fermented foods and beverages such as koumiss, kimchi, zlatar cheese and kung-som; however, some bacteria have been isolated from fresh ocean fish, fish intestine and infant faeces [1, 12, 13, 14, 16, 42, 43, 44].

Glutamic acid decarboxylase has also been identified in yeasts such as Saccharomyces cerevisiae and Kluyveromyces marxianus isolated from fermented product [16, 45]. S. cerevisiae had lower activity than L. plantarum, this may be caused by the utilization of GABA by S. cerevisiae as nitrogen source [16, 18]. However coculture L. plantarum and S. cerevisiae had highest activity to produce GABA than single culture L. plantarum nor S. cerevisiae in mulberry juice [16]. Wild yeast, such as Kazachstania unispora, Sporobolomyces carnicolor, Sporobolomyces ruberrimus, Nakazawaea holstii and Pichia sclothy, isolated from wild flowers, also have GAD activity [15].

Aspergillus oryzae is a mould used to ferment rice-koji fermentation for brewing sake. A. oryzae generates GABA [18]. Rhizopus oligosporus and R. oryzae are moulds used to prepare tempe (fermented soybean) generating 1.770 mg/100 g GABA for R. microsporus var. oligosporus IFO 32002 and 770 mg/100 g GABA for R. oryzae IFO 4705 and R. oryzae IFO 5438 [19]. LABs are the most studied GABA producers, because they are economically viable as starters and generate higher GABA than other producers [3].

A number of factors, namely temperature, pH, substrate and culture time influence the amount of GABA produced during microbial fermentation (Table 2). According to [1], the optimum fermentation temperature for GABA synthesis is 30 °C, whereas according to [22] is 37 °C. The optimal conditions for GABA synthesis by L. brevis are pH 3.5–5, in GM broth containing 1% glucose, 2.5% yeast extract, 2 ppm Tween 80, 2 ppm CaCO3, MnSO4, 10 µM PLP and 650 mM MSG [46]. However, according to Lim et al. [12], the optimal conditions for GABA synthesis by Enterococcus faecium are pH 7.74, with substrate containing 2.14% (w/v) maltose, 4.01% (w/v) treptone and 2.38% (w/v) MSG. The growth of E. faecium increased proportionally to the initial pH, of which the experimental pH is in the range 4–8. Likewise, the formation of GABA increased with the increasing number of E. faecium, but at a pH of more than 7.5 the formation of GABA decreased.

pH is a crucial factor in GABA biosynthesis, GAD in LAB is only active under acidic conditions and loses its activity at a pH > 5 [8]. GAD activity is optimum at pH 4.5 [22]. GABA biosynthesis causes an increase in pH and acid is adding during the fermentation process to maintain pH [8]. In addition, the activities of enzymes that decompose GABA, such as GABA transaminases and SSADH [2], must be considered [18]. The optimum pH for fermentation varies: for L. plantarum pH 5 and L. brevis pH 3.5–5, with an optimum at 4.74, are optimal [12, 20, 46].

During fermentation, Saccharomyces cerevisiae may consume GABA using SSADH at pH 8.40, thereby reducing the amount of GABA produced [18]. In Pseudomonas, GABA is used as a substrate at pH 8.5 by GABA transaminase, which is inhibited by adding a buffer [8].

Media composition also affects GABA biosynthesis. GABA production by L. paracasei and L. brevis increases upon adding glutamate [8]. Addition of glutamate to yogurt-sake fermented by Streptococcus thermophilus Hp increases the concentration of GABA. The use of compared to sake, amazake, a substitute for sake, produces a higher concentration of GABA [22] The addition of glutamate produces curd that is rich in GABA [20].

Fermentation temperature is important for GABA production [16]. Fermentation temperature affects the growth of microorganisms. For L. brevis the optimum temperature is 30 °C, S. thermophilus Hp 37 °C and L. plantarum 30–36 °C [1, 16, 20, 22, 23].

![Figure 1. Metabolic pathway of GABA production from the TCA cycle](image-url)
Time of fermentation influences GABA production, i.e., longer the fermentation time, higher is the GABA concentration. *L. plantarum* DSM19463 and *L. paracasei* NFRI 7415 need 72 and 144 h to produce 4.83 mM and 60 mM GABA, respectively [8]. *L. plantarum* needs 84 h to produce 211.169 mM GABA in *dadih* [20] and *L. lactis* needs 24 h to produce 1,031 mg/kg in mulberry beer [16].

γ-aminobutyric acid synthesis by microorganisms is affected by temperature, pH, substrate and culture time [1, 8, 12, 16, 18, 20, 22, 46]. Numerous studies have shown that the addition of glutamate can increase the formation of GABA [8, 20, 22]. Apart from affecting the amount of GABA, these factors also affect the degradation of GABA by GABA-AT and SSADH which are active at pH above 8 [8], [18]. So that fermentation process optimisation is needed.

### 4. Optimisation of γ-aminobutyric acid production in fermented foods and beverages

The amount of GABA in some fermented foods and beverages is small. The fermentation process needs to be optimised to produce higher amounts of GABA. Optimisation studies have included stages such as (1) isolating and purifying microorganisms from fermented foods and beverages; (2) identifying GAD activity in the selected colony; (3) identifying the name of the microorganism that produced the highest amount of GABA; (4) optimising the growth of the selected microorganism; (5) and producing fermented foods and beverages using the selected microorganism under optimum growth conditions [22].

#### Table 1. γ-aminobutyric acid (GABA) production by microorganisms.

| Microorganism | Species | Amount of GABA | Reference |
|---------------|---------|----------------|-----------|
| LAB           | *Streptococcus thermophilus* Hp | 3,894 ± 132 μM | [22]      |
|               | *S. thermophilus* QUW-LYS1 | 2.905 g/L | [59]      |
|               | *Lactobacillus brevis* DPC6108 | 11.01–32.32 mg/mL | [10]      |
|               | *L. brevis* RK03 | 62.523 mg/L | [1]       |
|               | *L. brevis* FPA 3709 | 2.45 ± 0.30 mg/mL | [14]      |
|               | *L. brevis* HYE1 | 14.64–18.97 mM | [12]      |
|               | *L. brevis* IFO 12005 | 10.18 mM | [13]      |
|               | *L. paracasei* NFRI 7415 | 302 mM | [60]      |
|               | *L. fitzii* CS3 | 1,280–10,500 mg/kg | [61]      |
|               | *L. plantarum* C48 | 504 mg/kg | [23]      |
|               | *Bifidobacterium adolescentis* | <0.5 mM | [43]      |
| Yeasts        | *Kazachstania unispora* | ND | [15]      |
|               | *Sporobolomyces carneolus* | ND | [18]      |
|               | *Sporobolomyces ruberrimus* | ND | [16]      |
|               | *Nakazawaea holstii* | ND | [16]      |
|               | *Pichia scolyti* UL6-1 | 134.4–136.5 μg/mL | [41]      |
|               | *Pichia scolyti* 402-JB-1 | 179.2–200.8 μg/mL | [12]      |
|               | *Saccharomyces cerevisiae* | ND | [16]      |
| Moulds        | *Aspergillus oryzae* | ND | [18]      |
|               | *Bhispora microspora var. oligosporus* IFO 32002 | 1,740 mg/100 g | [19]      |
|               | *Bhispora oryzae* IFO 4705 | 770 mg/100 g | [19]      |
|               | *Aspergillus oryzae* | 83.2 μg/g | [62]      |

*ND = not defined.*

#### Table 2. Optimum fermentation conditions.

| Microorganism | Source | Fermentation Media | γ-aminobutyric acid production | Reference |
|---------------|--------|--------------------|-------------------------------|-----------|
| *Lactobacillus brevis* RK03 | Ocean fish from the fish markets in Taiwan | GM broth containing 1% glucose; 2.5% yeast extract; 2 ppm each of CaCO3, MnSO4 and Tween 80 and 10 μM pyridoxal phosphate (PLP) | 62,523 mg/L | [1] |
| *L. brevis* FPA 3709 | Fish intestine | MRS broth, 5% mono sodium glutamate (MSG), at 37 °C for 48 h | 2.45 ± 0.30 mg/mL | [14] |
| *L. brevis* DPC6108 | Infant faeces | MRS supplemented with 30 mg/mL MSG, cultured anaerobically at 37 °C for 72 h | 28.02 mg/mL | [10] |
| *L. fermentum* NBRC 3956 | Fermented Thai foods | MRS broth, pH 6.5, 40 °C and 10 d incubation | 12 mg/mL | [63] |
| *L. paracasei* NFRI 7415 | Funa-sushi (fermented fish from Japan) | MRS broth with pyridoxal phosphate, 500 mM glutamate, pH maintained at 5.0, 30 °C | 302 mM | [60] |
| *L. pentosus* SS6 | Fermented mulberry fruits | 10% saccharose, 6% peptone, 1.6% K2HPO4, 1% L-sodium glutamate and a 60% water, fermented for 36 h at 35 °C | ND | [7] |

*ND = not defined.*
Isolation and purification aim to identify one indigenous microorganism and test its ability to produce the desired compound, which is GABA in this case. GABA producers can be isolated from fermented foods or beverages [7, 11, 21, 22, 47].

The stages for microorganism isolation include sample preparation, inoculation and incubation. Thereafter, the LAB colony with a clear area around it in MRS (de Man Rogosa and Sharpe) agar media is selected and screened for its ability to produce GABA. The selection of microorganisms that produce high levels of GABA is needed by the fermented food industry, especially for functional food production [11]. Microorganisms isolated from fermented foods and beverages are Lactobacillus plantarum, L. pentosus S66, L. brevis, L. brevis, Leuconostoc mesenteroides, L. lactis and Streptococcus thermophilus Hp [7, 9, 11, 16, 20, 22].

*Kimchi* is a fermented South Korean food that is traditionally made from vegetables such as banchu cabbage (Chinese cabbage), cucumber, radish and green onion with red paper powder, garlic, ginger and jeotgal (fermented seafood) [48, 49, 50]. *Kimchi* is fermented by LAB, which have GAD activity. *Lactobacillus plantarum* is an LAB with GAD activity and is predominantly used for *kimchi* preparation. *L. brevis, Leuconostoc mesenteroides, Leuconostoc lactis* and Weissella viridescens can also be isolated from kimchi and have GAD activity [11].

*Lactobacillus plantarum* can also be isolated from fermented buffalo milk called *dadh*, which originates from West Sumatra [16, 20]. *Dadh* is fermented in bamboo covered with banana leaves. Fermentation is done by several LAB, such as *L. brevis*, *L. paracasei*, *L. pentosus*, *L. plantarum* and *Lactococcus lactis* [51]. Harmentis et al. [20] isolated 10 LAB from *dadh*, of which *L. plantarum* N5 could generate the highest amount of GABA, compared to the others.

LAB with GAD activity is also found in zlatar cheese and yogurt-sake. Twenty-five strains of LAB have been isolated in zlatar cheese, of which 15 have GAD activity. *L. brevis* BGZLS10-17 is a LAB with GAD activity and the potential as a probiotic [9]. Moreover, 11 strains of LAB have been isolated from yogurt-sake and the highest GABA producer is identified as *S. thermophilus* Hp, which produced 3,000 μM GABA after 54 h of incubation [22].

As a small amount of GABA is produced by the spontaneous fermentation of food and beverages, several optimisations have been done. Table 3 shows the optimisations done for fermenting foods and beverages. Tempe is indigenous Indonesian food made from soybean that is rich in glutamic acid and is fermented using *Rhizopus* spp. Fermentation of soybean by *R. microsporus var. oligosporus* IPO 32002 at 30 °C for 20–22 h and 20 h under aerobic and anaerobic conditions, respectively, generates the highest content of GABA, at 1,740 mg/100 g (dry basis) [19].

Optimisations have also been done with *L. plantarum* C48 and *Lactococcus lactis* subsp. *lactis* PU1 for sourdough bread preparation. Optimisation fermentation requires *L. plantarum* C48 at 5 × 107 CFU/g with an addition of 0.1 mM PLP for 24 h at 30 °C. Fermentation of buckwheat, amaranth, chickpea and quinoa flour at a ratio of 1:1:5.3:1 under these conditions generates 504 mg/kg GABA [23]. For the preparation of *kung-som* or fermented shrimp, which originates from Thailand, *Lactobacillus futsaii* CS3, used as starter at 8 log CFU/g, supplemented with 0.5% MSG, generates 10.130 mg/kg GABA [42].

*Streptococcus thermophilus* has GAD activity, was isolated from dairy products and is used as a starter in fermented milk and yogurt. The use of *S. thermophilus* in fermented milk generates 2.8 g/L GABA after 48 h of fermentation. Higher levels of GABA can be achieved by co-culturing *L. rhamnosus*, which produces 8.3 g/L of GABA [44]. In yogurt, *S. thermophilus* APC151 used as starter, with 2.25 mg/mL MSG, generates 2.45 ± 0.30 mg/mL GABA [22].

Table 3. Optimisation of fermentation process in fermented food.

| Fermented Product [Reference] | Microorganism | Source | Fermentation condition | γ-aminobutyric acid production |
|-------------------------------|---------------|--------|------------------------|-------------------------------|
| Tempe [19]                    | *Rhizopus microsporus var. oligosporus* IPO 32002 and 32003 | Ikeda Food Res. Co. | Aerobic cultivation at 30 °C for 20–22 h and anaerobic cultivation at 30 °C for 20 h | 1,740 mg/100 g (Dry Basis) |
| Sourdough [22]                | *Lactobacillus plantarum* C48 | Cheese | Flour supplemented with 0.1 mM pyridoxal 5 phosphate, starter 5 × 107 CFU/g, at 30 °C for 24 h | 504 mg/kg |
| Kung-som [42, 61]             | *L.* futsaii CS3 | Kung-som | Starter culture 8 log CFU/g, supplemented with 0.5% MSG | 10.130 mg/kg |
| Yogurt-sake [22]              | *Streptococcus thermophilus* Hp | Yogurt-sake | T 37 °C for 5 d, supplemented with 380 μM glutamate | 424 μM |
| Yogurt-amazake [22]           | *S. thermophilus* Hp | Yogurt-sake | T 37 °C for 5 d | 1,096 μM |
| Yogurt [52]                   | *S. thermophilus* APC151 | Digestive tract of fish | Milk consisted of 14% (w/v) skim milk, supplemented with 2.25 mg/mL MSG at 42 °C for 48 h. | 2 mg/mL |
| Fermented milk [44]           | *S. thermophilus* | Koomiz dairy products | T 43 °C for 48 h, supplemented with 10% skim milk powder and 15 g/L MSG | 8.3 mg/L |
| Black soybean milk [14]       | *Lactobacillus brevis* FPA 3709 | Fish intestine | T 37 °C, t 48 h, supplemented with 1% MSG, 1% brown sugar and 0.1% peptone | 2.45 ± 0.30 mg/mL |
| Shochu kazu [13]              | *L. brevis* IFO-12005 | ND | Shochu kazu (pH 5.2) with 1% inoculum and 10.50 mM free glutamic acid, at 30 °C for 2 d | 10.18 mM |
| Mulberry beer [16]            | *Saccharomyces cerevisiae* SC125 | Shichuan Paocai | T 30 °C, t 72 h, supplemented with 5 g/L glutamate | 2.42 g/L |
|                               | *L. plantarum* BC114 | Fermented vegetable |  |

**ND** = not defined.
glutamate, generates 2.42 g/L of GABA. The fermentation also increases volatile compounds and increases the concentration of fruity esters [16].

There has been optimisation of GABA formation in fermented products. The optimisation is done by conditioning the fermentation process according to the optimal conditions of selected indigenous microorganisms as starter culture which has GAD activity. Also, the addition of PLP, glutamate, and MSG were used to increase the concentration of GABA in fermented products [16, 22, 23, 42, 52]. The amount of GABA in fermented products needs to be considered in order to provide its functionality.

## 5. Functional effects of γ-aminobutyric acid

GABA is a bioactive material, found in the brain, and acts as an inhibitory neurotransmitter. Studies show that GABA performs multiple physiological functions (Table 4).

### Table 4. Functional effect of γ-aminobutyric acid (GABA).

| Functional effect | Object | GABA dosage | Reference |
|-------------------|--------|-------------|-----------|
| Antihypertensive   | Rats   | Single dose of 0.05-5.00 mg/kg | [25] |
|                   |        | Single dose of GABA-rich tomato containing 3.6-17.9 mg of GABA | [17] |
|                   |        | Single dose of mulberry leaf containing 3.8 ± 0.71 mg/g of GABA (20 mg/kg body weight) | [6] |
|                   |        | Daily intake of fermented beans containing 0.4-2 g/kg GABA and nattokinase for 8 weeks | [53] |
|                   | Human  | Daily intake of 50 g cheese containing 16 mg of GABA for 12 weeks | [26] |
|                   |        | Twice daily intake of GABA-rich Chlorella containing 20 mg of GABA for 12 weeks | [54] |
| Antidiabetic       | Rats   | Daily intake of tea extracts containing 3.01 or 30.1 μg of GABA for 6 weeks | [55] |
|                   |        | ND | [29] |
|                   |        | Daily intake of 6 mg/mL GABA in drinking water for 6 weeks | [57] |
|                   | Human  | Twice daily intake of GABA and injection of GAD | [64] |
|                   |        | Daily intake of 2 g of GABA once or three times/d for 7 d | [56] |
| Renal Protection   | Rats   | Dose of 100 or 500 mg/kg daily via a stomach tube for 100 consecutive days | [58] |
| Anticancer         | Human  | ND | [28] |
| Relaxation         | Human  | Dose of 100 mg of GABA in 200 mL distilled water | [24] |
| Immunity enhancer  | Human  | ND | [24] |

*ND = not defined.

Although studies have been carried out to identify microbiological sources of GABA and maximize production through fermentation, there is not enough information available on the production of GABA in fermented foods and beverages at an industrial scale. Therefore, the process of scale-up needs to be completed. It may present a new challenge, such as the need for microorganisms which produce higher GABA in the pilot or mini-scale for the subsequent mass production.

## 6. Opportunity and challenges

GABA-enriched fermented foods and beverages can potentially become a trend as functional foods. The processing of GABA by microorganisms in fermented foods and beverages is simple and does not require high production costs during the purification process. Thus, both the industry and the consumer can receive benefits.

Although studies have been carried out to identify microbiological sources of GABA and maximize production through fermentation, there is not enough information available on the production of GABA in fermented foods and beverages at an industrial scale. Therefore, the process of scale-up needs to be completed. It may present a new challenge, such as the need for microorganisms which produce higher GABA in the pilot or mini-scale for the subsequent mass production.

## 7. Concluding remarks

γ-aminobutyric acid is a bioactive agent found in plants, animals and microorganisms that has potential functional effects as an antihypertensive, antidiabetic, anticarcinogenic, antidepressant and immune enhancer. GABA production is performed by fermentation using selected microorganisms. LAB, such as *Lactobacillus plantarum*, *L. brevis* and *Streptococcus thermophilus* are used as starters in fermented foods and beverages to produce GABA. Temperature, pH, substrate, culture time and L-glutamate content during the fermentation process affect GABA synthesis. So those factors need to be watched. GABA-enriched fermented foods and beverages can be potentially developed as functional foods. However, optimisation and scale-up are needed to ensure that production at a large scale is optimal.

Extensive details, in particular on aspects of clinical and pre-clinical studies on the application of GABA from fermented foods and beverages, should also be of concern. Given the long-term effects of fermented products consumption, and their role in improving the health of those who eat them.
Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This work was supported by Universitas Padjadjaran (Academic Leadership Grant).

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] C. Wu, Y.-H. Hsieh, J.-M. Kuo, S.-J. Liu, Characterization of a potential probiotic Lactobacillus brevis RK03 and efficient production of γ-amino-butyric acid in batch fermentation, Int. J. Mol. Sci. 19 (143) (2018) 1–16.

[2] J. Hong, K. Kim, Biochemical and Biophysical Research Communications Crystal structure of γ-amino-butyrate aminotransferase in complex with a PLP-GABA adduct from Corynebacterium glutamicum, Biochem. Biophys. Res. Commun. 514 (3) (2020) 601–606.

[3] M. Diana, J. Queluz, M. Rafecas, ‘Gamma-aminobutyric acid as a bioactive compound in foods: a review, J. Funct. Foods 10 (2014) 407–420.

[4] M. Zhao, Z.W.Y. Ma, Y. Wen-xia, C.Z.Y. Li, L.X. Xiao-ting, Z. Hong-jie, Determination and comparison of γ-amino-butyric acid (GABA) content in Pu-erh and other types of Chinese tea, J. Agric. Food Chem. 59 (2011) 3641–3648.

[5] H. Chen, H. Xuanhui, J.L. Yan Liu, H. Qingyong, Z. Cuiling, W. Benjun, Z. Ye, W. Jie, Extraction, purification and anti-fatigue activity of γ-amino-butyric acid from mulberry (Morus alba L.) leaves, Sci. Rep. 6 (18953) (2016) 1–15.

[6] N. Yang, K. Jou, C. Tseng, Antihypertensive effect of mulberry leaf aqueous extract containing γ-amino-butyric acid in spontaneously hypertensive rats, Food Chem. 132 (4) (2012) 1796–1801.

[7] Y. Zhong, S. Wu, F. Chen, M. He, J. Jin, ‘Isolation of high γ-amino-butyric acid-producing lactic acid bacteria and fermentation in mulberry leaf powders, Experimental and Therapeutic Medicine 18 (2019) 147–153.

[8] D. Kashni, R. Zanan, S. John, K. Khandagale, γ-Aminobutyric Acid (GABA): Biosynthesis, Role, Commercial Production, and Applications, first ed., 2018, pp. 413–452, 57, chapter 13.

[9] S.S. Bajic, J. Djokic, M. Dinic, K. Veljovic, N. Golic, GABA-producing natural dairy compound in foods: a review, J. Funct. Foods 10 (2014) 407–420.

[10] A.D. Abuos, S. Hijbaghiguchi, K. Horie, M. Kim, H. Hatta, Y. Yokogoshi, Relaxation and immunity enhancement effects of γ-amino-butyric acid (GABA) administration in humans, Biosc. Biotechnol. Biochem. 26 (2006) 201–208.

[11] K. Hayakawa, M. Kimura, K. Kauha, K. Matsumoto, H. Sannawa, ‘Effect of a γ-amino-butyric acid-enriched dairy product on the blood pressure of spontaneously hypertensive and normotensive Wistar–kyoto rats, Br. J. Nutr. 92 (2004) 411–417.

[12] K. Pouilot-mathieu, C. Gardner-fortier, S. Lemieux, D.S. St-gelais, C.P. Champagne, J. Villemard, Effect of cheese containing gamma-amino-butyric acid-producing lactic acid bacteria on blood pressure in men, PharmaNutrition 1 (2013) 141–148.

[13] H.M. Schuller, H.A.N. Al-wadei, M. Majidhi, Gamma-amino-butyric acid, a potential tumor suppressor for small airway-derived lung adenocarcinoma, Carcinosgenesis 29 (10) (2008) 1979–1985.

[14] Q. Huang, C.Z.C. Liu, Gamma-amino-butyric acid binds to GABA B receptor to inhibit cholangiocarcinoma cells growth via the JAK/STAT3 pathway, Dig. Dis. Sci. 58 (2013) 734–743.

[15] E. Adeaghe, A.S. Ponery, GABA in the endocrine pancreas: cellular localization and function in normal and diabetic rats, Tissue Cell 34 (1) (2002) 1–6.

[16] R. Dhabal, V.K. Bajpai, K. Baek, ‘Production of gamma (γ – amino-butyric acid) by Microorganisms: a review, Braz. J. Microbiol. (2012) 1230–1241.

[17] S. Rohohnejad, K. Mallikarjunan, M. Koushab, U. States, Gamma-Amino-Butyric Acid Production of GABA by Plants, Encyclopedia of Food Chemistry, 2018, pp. 528–534.

[18] H. Li, Y. Cao, Lactic acid bacterial cell factories for gamma-amino-butyric acid, Amino Acids 39 (2010) 1107–1116.

[19] M. Watanabe, K. Maenmura, K. Kanbara, T. Tamayama, H. Hayasaki, GABA and GABA receptors in the central nervous system and other organs, Int. Rev. Cytology 213 (2002) 1–47.

[20] P. Hajej, S. Jinap, Fermented shrimp products as source of umami in southeast asian journal of nutrition & foods sciences, J. Nutr. Food Sci. (2012) 1–5.

[21] Y. Suzuki, Y. Fujitani, T. Nakagawa, K. Kurosu, T. Hanazaki, Development of a metabolic regulatory network in Escherichia coli for purposeswitching from cell growth mode to production mode in direct GABA fermentation from glucose, Metab. Eng. (2017) 1–17.

[22] A.W. Bown, B.J. Shelp, ‘Trends in plant science spotlight does the GABA shunt regulate eustolic GABA? Trends in plant science, Trends Food Sci. Technol. 83 (2019) 129–137.

[23] A.R. Rai, A. Pandey, D. Sahoo, Biotechnological potential of yeasts in functional food industry, Trends Food Sci. Technol. 83 (2019) 129–137.

[24] D.H. Kim, C. Dasagrandhi, S.K. Park, S.H. Eom, Optimization of gamma-amino-butyric acid production using sea tangle extract by lactic acid bacterial fermentation, J. Sci. Food. Technol. (Lebensmittel-Wissenschaft -Technol.) 90 (2019) 636–642.

[25] W. Liao, C. Wang, Y. Shyu, R. Yu, K. Ho, Influence of preprocessing methods and fermentation of adzuki beans on ε-amino-butyric acid (GABA) accumulation by lactic acid bacteria, J. Funct. Foods 5 (3) (2013) 1108–1115.

[26] S. Kumar, N.S. Punekar, The metabolism of GABA (GABA) in fungi, Mycol. Res. 104 (4) (1997) 403–409.

[27] S.M. Han, J.S. Lee, Production and its anti-hyperglycemic effects of γ-amino-butyric acid from the wild yeast strain Pichia silvicola UL1-6 and Sporobolomyces carnosii GAL02-B1, Mycobiology 45 (3) (2017) 199–203.

[28] C. Sanschart, N. Watthanasakphul, O. Boomsong, T. Nguyen, Tuna condensate as a promising low-cost substrate for glutamic acid and GABA formation using Candida rugosa and Lactobacillus futsaii, Process Biochem. 70 (2018) 29–35.

[29] P. Strandsvold, K.H. Kim, D. Terekhova, J.K. Liu, A. Sharma, J. Levering, D. McDonald, D. Dietrich, T.R. Ramadhar, A. Lekbua, N. Mroue, C. Liston, E.J. Stewart, M.J. Dubin, K. Zengler, R.A. Gilbert, J. Clardy, K. Lewis, Eradicating modulation of human gut microbes by GABA-modulating bacteria of the human gut microbiota, Nat. Microbiol. (2018).

[30] M. Han, Use of Streptococcus thermophilus for the in situ production of γ-amino-butyric acid-enriched fermented milk, J. Dairy Sci. 103 (201) (2020).
[45] G. Perpetuini, R. Tofalo, F. Tittarelli, N. Battistelli, G. Suzzi, R. Tofalo, γ-aminobutyric acid production by Kluyveromyces marxianus strains, J. Appl. Microbiol. (2020).

[46] Q. Wu, N.P. Shah, Restoration of GABA production machinery in Lactobacillus brevis by accessible carbohydrates, anaerobiosis and early acidification, Food Microbiol. 69 (2018) 151–158.

[47] R. Tofalo, G. Perpetuini, N. Battistelli, A. Pepe, A. Ianni, G. Martino, G. Suzzi, Accumulation of γ-aminobutyric acid and biogenic amines in a traditional raw milk cheese’s cheese, Foods 8 (401) (2019) 1–13.

[48] N. Hongu, A.S. Kim, A. Suzuki, H. Wilson, K.C. Tsui, S. Park, Korean kimchi: promoting healthy meals through cultural tradition, J. Ethn. Foods 4 (3) (2017) 172–180.

[49] D. Jang, J. Rhan, H. Jeong, K. Kim, D. Young, Discussion on the origin of kimchi, representative of Korean unique fermented vegetables, J. Ethn. Foods 2 (3) (2015) 126–136.

[50] K. Park, J. Jeong, Y. Lee, J.W.D. Iii, Health benefits of kimchi (Korean fermented vegetables) as a probiotic food, J. Med. Food 17 (1) (2014) 6–20.

[51] H. Rizqiati, Nurwantoro, S. Mulyani, A. Febrisiantosa, Isolation and identification of lactic acid bacteria from pampangan buffalo milk of South sumatera Indonesia, World J. Pharmaceutical Life Sci. 2 (4) (2016) 1–12.

[52] D.M. Linares, T.F.O. Callaghan, P.M.O. Connor, R.P. Ross, C. Stanton, Streptococcus thermophilus APCI51 strain is suitable for the manufacture of naturally GABA-enriched bioactive yogurt, Front. Microbiol. 7 (1876) (2016) 1–9.

[53] K. Suwanmanon, P. Hsieh, ScienceDirect Effect of γ-aminobutyric acid and nattokinase-enriched fermented beans on the blood pressure of spontaneously hypertensive and normotensive Wistar e Kyoto rats, J. Food Drug Anal. (2014) 1–7.

[54] M. Shimada, T. Hasagawa, C. Nishimura, H. Kan, T. Kann, T. Nakamura, T. Matsubayashi, Anti-hypertensive effect of γ-aminobutyric acid (GABA) rich chlorella on high-normal blood pressure and borderline hypertension in placebo-controlled double blind study, Clin. Exp. Hypertens. 31 (2009) 342–354.

[55] C.Y. Huang, W.W. Kuo, H.F. Wang, C.J. Lin, Y.M. Lin, J.L. Chen, C.H. Kuo, St. Mulyani, A. Febrisiantosa, Isolation and identification of lactic acid bacteria from pampangan buffalo milk of South sumatera Indonesia, World J. Pharmaceutical Life Sci. 2 (4) (2016) 1–12.

[56] J. Li, Z. Zhang, X. Liu, Y. Wang, F. Mao, J. Mox, X. Xu, D. Jiang, Y. Wan, J.Y. Lv, G. Cao, J. Zhang, N. Zhao, M. Atkinson, D.L. Greiner, G.J. Prudhomme, Z. Jiao, Y. Li, Q. Wang, Study of GABA in healthy Volunteer: pharmacokinetics and pharmacodynamics, Front. Pharmacol. 6 (260) (2015) 1–9.

[57] W. Liu, D.O. Son, H.K. Lau, Y. Zhou, G.J. Prud, G.M. Leggio, Combined oral administration of GABA and DPP-4 inhibitor prevents beta cell damage and promotes beta cell regeneration in mice, Front. Pharmacol. 8 (262) (2017) 1–10.

[58] S. Sasaki, T. Yokozawa, E.J. Cho, S. Owada, M. Kim, Protective role of γ-aminobutyric acid against chronic renal failure in rats, J. Pharm. Pharmacol. (2006) 1515–1525.

[59] H. Liu, J. Zhang, W.Q. Yang, Z.Y. Liu, X. Chen, H. Guo, B.Y. Liu, C.G. Zang, Y.C. Liu, J.C. Liu, H. Guan, Bio-synthesis of GABA by Streptococcus thermophilus QYW-LYS1 isolated from traditional fermented yoghurt, Adv. Mater. Res. 885 (2014) 401–404.

[60] N. Komatsu, J. Shima, S. Kawamoto, H. Momose, Production of γ-aminobutyric acid (GABA) by Lactobacillus paracasei isolated from traditional fermented foods, Food Microbiol. 22 (2005) 497–504.

[61] C. Sanchart, O. Rattanaporn, D. Haltrich, P. Phukpattaranont, S. Maneerat, Enhancement of gamma-aminobutyric acid (GABA) levels using an autochthonous Lactobacillus futsaii CS3 as starter culture in Thai fermented shrimp (Kung-Som), World J. Microbiol. Biotechnol. 33 (8) (2017) 1–12.

[62] S. Cai, F. Gao, X. Zhang, Evaluation of γ-aminobutyric acid, phytate and antioxidant activity of tempeh-like fermented oats (Avena sativa L.) prepared with different filamentous fungi, J. Food Sci. Technol. (2012).

[63] S. Woraharn, N. Lailerd, B.S. Sivamaruthi, Screening and kinetics of glutaminase and glutamate decarboxylase producing lactic acid bacteria from fermented Thai foods Screening and kinetics of glutaminase and glutamate decarboxylase producing lactic acid bacteria from fermented Thai foods, Food Sci. Technol. Campinas 34 (4) (2014) 793–799.

[64] H.M. Choat, A. Alexandra, G.J. Mick, K.E. Heath, H.M. Tae, G. McGwin Jr., K.L. McCormick, Effect of gamma-aminobutyric acid (GABA) or GABA with glutamic acid (GABA) against chronic renal failure in rats, J. Food Sci. Technol. Campinas 34 (4) (2014) 793–799.