Original Research Article

Research progress based on bioenrichment technology of γ-aminobutyric acid

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Abstract: Non-protein amino acid of γ-aminobutyric acid (GABA) plays an important role in the human nervous system. GABA has revealed numerous physiological benefits in the medical and pharmaceutical fields in humans. It is regarded as an edible alternative treatment for the prevention and treatment of many diseases. As a result, GABA-rich functional foods are highly favored by consumers. Therefore, in order to meet the demand for healthy food, the use of effective and safe enrichment methods to increase the content of GABA in food has received much attention. The content of GABA in natural foods, bioenrichment techniques, and the health benefits of GABA-rich foods were discussed. In addition, the shortcomings and future challenges of GABA bioconcentration technology were discussed, in order to provide a new idea for the investigation of GABA enrichment technology.

Keywords: GABA; nutrition; processing; bioactive compound; functional food

1. Introduction

Four-carbon non-protein amino acid of γ-aminobutyric acid (GABA), with chemical name of 4-GABA[1], exists naturally in animals, plants, and microorganisms, and has a variety of important physiological functions[2]. It is reported that it mainly exists in the central nervous system of vertebrates as an inhibitory neurotransmitter[3] and plays an important role in regulating synaptic transmission, promoting neuron development, relieving stress, and preventing depression[4–6]. It is worth noting that the various biological activities of GABA have become a hot spot in medical and pharmaceutical research, including preventing nerve cell damage, lowering blood sugar, lowering blood pressure, and improving sleep, as well as anti-inflammatory, antioxidant, and antidepressant activities[7–9]. In addition, GABA can also protect the liver, kidneys, and intestines, preventing damage caused by toxins[10,11].

Based on the numerous health benefits of GABA, healthcare foods rich in GABA have been vigorously developed and are widely sought after by consumers, such as rice, dairy products, tea, etc.[12,13], However, the GABA content in natural foods is generally low[14]. Under normal dietary intake, GABA intake is difficult to achieve significant health benefits. In addition, although GABA has good thermal stability, thermal decomposition will still occur under heat treatment above 105 °C, resulting in a decrease in its content[15]. It is relatively difficult to isolate and extract GABA from natural products. The current preparation methods of GABA are mainly divided into chemical methods and biological methods, of which biological preparation methods can be subdivided into plant enrichment methods, microbial fermentation methods, and emerging technologies. Since chemical preparation may involve toxic reagents, the products may have potential safety hazards, so chemically synthesized GABA cannot be used as a food additive, nor can it be used in samples. Therefore, in this article, the technologies involved in the current GABA bioconcentration method were reviewed, including germination, various stress treatments (heat and moisture treatment, cold and heat stress, hypoxia, and salt stress), microbial fermentation, and emerging technologies. Furthermore, the challenges

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faced in the application of GABA enrichment technology were also discussed, aiming to provide a theoretical basis for food researchers and industrial personnel to develop new functional foods rich in GABA.

2. Content of GABA in natural foods

GABA is widely distributed in animals, plants, and microorganisms. In animals, GABA exists almost exclusively in nervous tissues, with the content in brain tissue being approximately 100.0–600.0 mg/100 g[16], but it is not suitable for use in food processing. Plant and microbial sources of GABA mainly include cereals[17–29], beans[30–38], fruits[39–46], vegetables[39,40,47–50], tea[51–56] and edible fungi[57–60] (as shown in **Figure 1**). Legume seeds generally contain higher levels of GABA due to the presence of glutamic acid (Glu, the precursor of GABA). Among them, the content of GABA in kidney beans can reach 69.2 mg/100 g[36]. Among cereals, barley and red rice have a higher GABA content[25,61]. Among fruits, the GABA content in litchi can reach 139.0–350.0 mg/100 g[40,43]. However, the GABA content in apples is only 0.0–0.5 mg/100 g[39,40]. Among vegetables, spinach and tomatoes have a higher GABA content. However, the GABA content in tomatoes is greatly affected by the variety and maturity period[47]. The GABA content in onions is only 0.1 mg/100 g. Among tea leaves, the GABA content of oolong tea can reach up to 97.0 mg/100 g. In addition, edible fungi also contain a large amount of GABA. The amino acid content of higher basidiomycete mushrooms, such as oyster mushrooms, enoki mushrooms, and shiitake mushrooms, is equivalent to that of animal protein, including all essential amino acids and non-essential amino acids, especially Glu. This may be the reason why mushrooms produce a large amount of GABA[58]. In summary, due to differences in food genotypes, growth climate, and culture conditions, GABA levels vary greatly between different food categories and even within the same food category. In order to meet the needs of human health, new research has been attempted to increase the content of GABA in food through safe and effective enrichment technology.

Figure 1. GABA content in natural foods.

3. Bioconcentration technology of GABA

In recent years, as people's awareness of the health benefits of GABA continues to increase, research on methods to increase the GABA content in food has increased. In order to effectively increase GABA levels in foods, a deep understanding of the different enrichment technologies applicable to various foods is required, as well as the basic enrichment mechanisms, advantages, and limitations of these technologies. These technologies include, but are not limited to, germination, heating and relative humidity control, stress treatments, microbial fermentation, and emerging technologies.

Currently, GABA enrichment technology mainly involves two main anabolic pathways (as shown in **Figure 2**). The primary synthesis pathway of GABA is the GABA branch pathway[62], where glutamate decarboxylase (GAD) catalyzes the irreversible decarboxylation of Glu to synthesize GABA in the cytoplasm. Subsequently, GABA is transferred into mitochondria and transaminated by GABA transaminase (GABA-T) to form succinic semialdehyde (Sus). Sus is subsequently oxidized to succinate (Suc) by NAD^+-dependent succinate semialdehyde dehydrogenase (SSADH), which subsequently enters the TCA cycle. Another GABA synthesis pathway is the polyamine metabolism pathway, in which arginine is converted to putrescine through a multi-step pathway. Putrescine is then converted to 4-aminobutyraldehyde by polyamine oxidase (PAO) or to spermidine, which is degraded to 4-aminobutyraldehyde and then dehydrogenated by the NAD^+-dependent 4-aminobutyraldehyde dehydrogenation (ABALDH) enzymes to be oxidized into GABA.

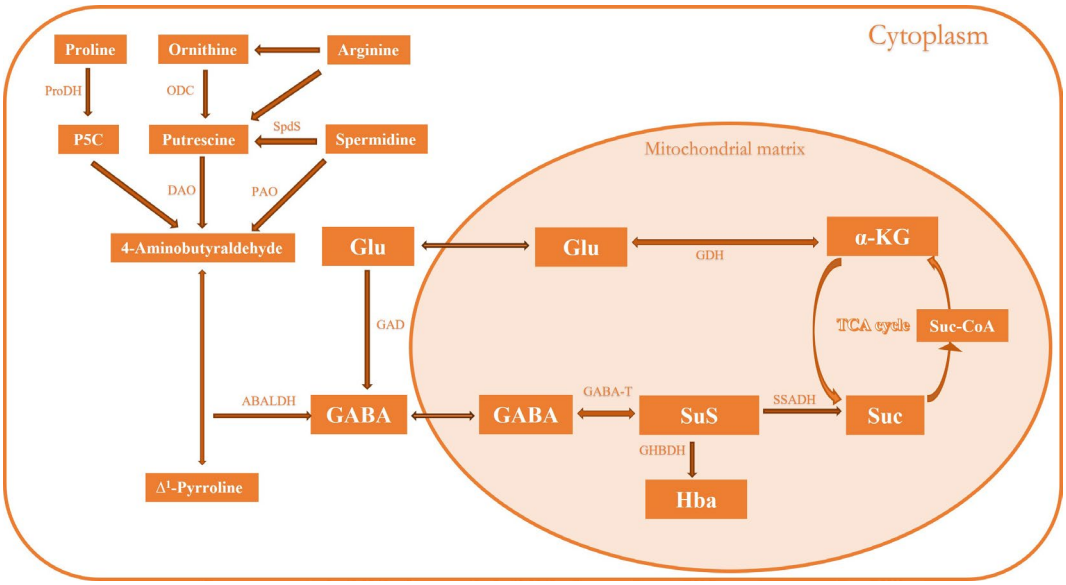

Figure 2. GABA synthesis metabolic pathway.
Note: P5C: 5-carboxydihydropyrrole; ProDH: proline dehydrogenase; ODC: ornithine decarboxylase; SpdS: spermidine synthase; DAO: diamine oxidase; PAO: polyamine oxidase; ABALDH: 4-aminobutyraldehyde dehydrogenation enzyme; Glu: glutamate; GDH: Glu dehydrogenase; GAD: glutamate decarboxylase; TCA: tricarboxylic acid; GABA-T: GABA transaminase; SSADH: succinate semialdehyde dehydrogenase; GHBDH: hydroxybutyrate dehydrogenase; Hba: hydroxybutyric acid; Suc: succinate; α-KG: α-ketoglutaric acid; Suc-CoA: succinyl-CoA; Sus: succinic semialdehyde.

3.1. Plant enrichment method

3.1.1. Heat and moisture treatment

The heat and relative humidity (HRH) treatment is a new method that can increase the GABA content in natural foods within a few hours (5–6 h) under low moisture (16.0–18.5%) and high temperature (50 ℃–70 ℃) conditions. As shown in **Table 1**, Ma et al.[31] and Ma et al.[63] collected 34 major mung bean varieties grown in eight different provinces in China for the HRH treatment and found that the average GABA content in mung beans after the HRH treatment increased 7.5 times that of the black mung bean varieties. The average GABA

level under the HRH treatment was higher than that of the green mung bean variety. In addition, a significant correlation was found between free Glu levels and GABA content ($p < 0.05$). This indicated that the effect of plant species on GABA accumulation ability was mainly caused by the effect of endogenous free amino acids in GABA channels. MB varieties rich in endogenous free Glu have better GABA accumulation potential. Similarly, 25 types of highland barley were treated with this method, and their GABA also showed varying degrees of enhancement, ranging from 26.9–76.3 mg/100 g[64]. Moreover, the results showed that the content of the substrate (polyamine) of the polyamine degradation pathway and the activities of key enzymes (diamine oxidase (DAO) and PAO) were not significantly related to the accumulation of GABA. This indicated GABA accumulation in highland barley under the HRH treatment. The main pathway was the GABA shunt pathway. It is worth noting that although the relevant research data on the use of HRH to enrich GABA are limited, Japan's Satake Machinery Co., Ltd., has been using the HRH treatment to produce GABA-rich rice, and the rice is currently on the market and widely sold[65].

Table 1. Various stress treatments for GABA enrichment.

Approach	Type	Optimum processing condition	GABA content	Growth multiple	Reference
HRH	Green beans	Treat at 70 ℃, 95% RH for 4 h	31.1 mg/100 g	7.5	[63]
	Green beans	Treat at 70 ℃, 95% RH for 4 h	113.1 mg/100 g	-	[31]
	Plateau barley	Treat at 65 ℃, 95% RH for 2.5 h	76.3 mg/100 g	2.1	[64]
Heat stress	Immature soybean seeds	Heating and drying at 40 ℃ for 72 h; vacuum drying at 20 ℃ for 4 h	447.5 mg/100 g	5.6	[66]
	Mulberry leaves	Dry at 130 ℃ and then bottle-fry for 25 min	401.0 mg/100 g	-	[67]
Cold stress	Soybean sprouts	Freeze at −18 ℃ for 12 h; freeze and thaw at 25 ℃ for 6 h	209.0 mg/100 g	7.2	[38]
	Mulberry leaves (BR 60)	Gradient cooling: store at 4 ℃, 0 ℃ and −1 ℃ for 10 h respectively	3.6 mmol/g	4.3	[68]
	Mulberry leaves (Lunbai No.1)	Gradient cooling: store at 4 ℃, 0 ℃ and −1 ℃ for 10 h respectively	3.8 mmol/g	11.8	[68]
	Mulberry leaves (Kangxuan 01-28)	Refrigerate at 4 ℃ for 2 d	5.1 mmol/g	33.9	[68]
Hypoxia	Agaricus bisporus	N_2 treatment for 24 h	-	13.9	[69]
	Green tea	CO_2 treatment for 6 h	-	1.5	[57]
	Tea	Vacuum treatment at 25 ℃ for 11 h	73.0 mg/100 g	20.0	[70]
	Tea	Vacuum treatment for 4 h	266.0 mg/100 g	16.6	[71]
	Rice bran	N_2 treatment at 40 ℃ for 8 h	171.5 mg/100 g	16.0	[72]
Salt stress	Sorghum	NaCl (41.07 mmol/L), pyridoxal phosphate (82.62 μmol/L), $CaCl_2$ (0.40 mmol/L) treated for 2 d (protect from light)	33.6 mg/100 g	1.3	[73]
	Barley seedlings	Soak at 25 ℃ for 6 h; incubate with NaCl (20 mmol/L) at 25 ℃ for 2 d	-	1.3	[74]
	Mulberry leaves	Sodium glutamate concentration 6.22 g/L, soaked at 25 ℃ for 18 h	377.0 mg/100 g	6.3	[75]
Two or more types of coercion	Maoye tea	Vacuum treatment for 3 h, aerobic treatment for 2 h, cycle 3 times	270.0 mg/100 g	22.5	[76]
	Mulberry leaves	Fresh leaves were laid out for 1.5 h, rolled for 30 min, anaerobically vacuum-treated for 8 h, and dried at 80 ℃	655.0 mg/100 g	-	[77]

3.1.2. Heat stress and cold stress treatments

During cold stress, freezing or freeze-thawing treatments may cause cell membrane tissue rupture and solute aggregation, thereby accelerating GABA synthesis. In the study by Yang et al.[38], bean sprouts treated with anoxia were frozen at −18 ℃ for 12 h and thawed at 25 ℃ for 6 h. The GABA content was significantly increased and was 7.2 times higher than that of unfrozen but hypoxia-treated bean sprouts. In another study[68], under low-temperature storage treatment, the GABA concentration in three mulberry leaf varieties of "Kangxuan 01-28", "Lunbai No. 1", and "BR 60" increased 33.9 times, 11.8 times, and 4.3 times, respectively,

compared with the initial concentration. This showed that under the same treatment, the enrichment effect of GABA varied greatly depending on the variety. The GAD activity of mulberry leaves under cold stress increased and the GABA-T activity decreased, which accelerated the synthesis rate of GABA from Glu, but the rate of conversion of GABA into succinic acid slowed down, thus promoting the enrichment of GABA in mulberry leaves. Although many studies reported that low-temperature stress produces high levels of GABA, Wang et al.[78] reported that the GABA content in tea roots decreased under a low-temperature treatment. This shows that high GABA content is also related to the low-temperature tolerance of plants.

In addition, some studies have shown that heat stress can promote the accumulation of GABA in plants. For example, Guo et al.[67] reported different drying methods (including drying first and then bottle frying, drying first and then pan frying, bottle frying and drying, secondary drying, bottle frying first and then drying, and pan frying and then drying, drying, stir-frying, and drying), and it was found that compared with untreated mulberry leaves, the GABA content of mulberry leaves after different drying methods increased by 259.0–401.0 mg/100 g. In addition, the GABA content of immature soybean seeds accumulated rapidly under thermal drying and reached a maximum at 40 ℃, which was 5.6 times that of untreated seeds. Under heat stress, GAD is expressed at high levels in seeds, but GABA-T and SSADH decrease rapidly[66]. This follows the same principle as the accumulation of GABA under cold stress; that is, both rely on the GABA shunt pathway to accumulate GABA.

3.1.3. Hypoxia treatment

It has been reported that hypoxia lowers the pH of the cytoplasm by 0.4–0.8, creating acidic conditions. In this acidic condition, GAD is activated and catalyzes the Glu decarboxylation reaction, producing more GABA to resist stress, reduce the content of toxic compounds, and regulate pH. Currently, anaerobic stress is mainly applied to mushrooms[69], tea[57], and some cereals[72] to enrich GABA. Liao et al.[70] treated tea leaves in a vacuum at 25 ℃ for 11 h, and the GABA content increased to 20 times its original value. This was due to the increased activity of GAD and DAO. Genes involved in GABA formation, such as CsGAD1 and CsGAD2, are significantly upregulated under hypoxic conditions. The concentrations of the substrates of the polyamine degradation pathway, namely putrescine and spermine, also increased via hypoxia. Liao et al.[70] treated tea leaves with aminoguanidine, which completely inhibited the activity of DAO under hypoxic conditions, but the GABA concentration only decreased by 25%. Therefore, it was speculated that under hypoxic conditions, about a quarter of the GABA formed in tea came from the polyamine degradation pathway[76]. In addition, when rice bran was treated with N_2 at 40 ℃ for 8 h, its GABA content increased significantly to 171.5 mg/100 g, which was 16.0 times the original[72]. Under hypoxic conditions, the activities of GAD and DAO increase, thereby increasing the GABA content of plants. Alternating hypoxia and oxygen treatments can also increase the GABA content of tea[76]. In summary, plants rely on both GABA shunting and polyamine degradation pathways to accumulate GABA in anoxic environments, but different plants mainly rely on different pathways.

3.1.4. Salt stress treatment

Salt stress is usually achieved by treating food raw materials with high concentrations of NaCl, $CaCl_2$, and sodium glutamate solutions, and different salt treatments lead to different GABA synthesis pathways. Wang et al.[79] treated chopped carrots with $CaCl_2$ to explore their effect on GABA content and its metabolic pathways. The results showed that exogenous $CaCl_2$ not only significantly promoted the activities of GAD, GABA-T, DAO, PAO, and aminoaldehyde dehydrogenase (AMADH) but also up-regulated the expression of DcGAD1, DcGAD2, DcGABA-T1, and DcPAO. This showed that $CaCl_2$ treatment can activate both the GABA shunt pathway and the polyamine degradation pathway. $CaCl_2$ appeared to be more effective in GABA shunt regulation. When Chi et al.[80] used exogenous $CaCl_2$ to treat carrot shreds, they also found that exogenous $CaCl_2$ induced GABA accumulation by activating the GABA shunt pathway. In addition, Bai et

al.[81] reported that NaCl stress also significantly increased the GABA content and GAD activity level of germinating millet. What is more noteworthy is that this study showed that NaCl stress mainly enriched GABA through the polyamine degradation pathway, but after adding $CaCl_2$, GABA accumulation was mainly synthesized through the GABA shunt. In general, salt stress can enrich GABA by activating enzymes related to GABA synthesis. However, it should be noted that high doses of these salts can lead to a reduction in GABA levels and GAD activity[73].

3.1.5. Germination

Germination enrichment technology can activate the activity of endogenous GAD enzymes, which catalyze the conversion of Glu into GABA. During the germination process, seed respiration is enhanced, the endogenous enzyme system is activated, and proteins are hydrolyzed into amino acids, etc. Previous studies have reported that for germination enrichment technology, the synthesis of GABA is mainly completed through the GABA shunt pathway rather than the polyamine degradation pathway[82]. Currently, germination enrichment technology is mainly applicable to cereal and legume crops.

Generally speaking, germination enrichment techniques involve a soaking process and germination at specific times and temperatures. Some researchers have done a lot of work to increase GABA content in different food sources, including exploring appropriate times and temperatures. Soybeans soaked in the dark for 10 h reached the maximum value of GABA (151.0 mg/100 g) on the third day of germination, which was 12.6 times that of raw soybeans[83]. As reported by Tiansawang et al.[30], seeds can activate GAD, which can convert Glu into GABA during germination. The rapid accumulation of GABA during soaking and early germination of mung beans and cowpeas is considered to be the response of young tissues to water stress[84,85].

Additionally, other studies have been conducted besides soaking the seeds in water. As shown in **Table 2**, adding additives during the germination process, including cellulase, electrolyzed water, mannose, Glu, and salts, can increase the content of GABA. Xie et al.[86] found that broccoli germinated by adding 1.0mmol/L mannose to a soaking solution, which contained high levels of GABA. Mannose can increase GABA synthase activity, inhibit GABA-T activity, and enrich GABA through two pathways: GABA shunting and polyamine degradation. In addition to the above conditions, changing ambient conditions, such as hypoxia or anoxia treatment and freezing treatment (as shown in **Table 2**), can further enhance the accumulation of GABA. Anaerobic stress was found to enhance the GABA accumulation ability during rice germination[87]. A recent study[88] showed that in black rice grains, the combination of cold stress and germination showed greater GABA accumulation than germination alone. As mentioned before, the activation of the GABA shunt pathway by cold stress may be the reason for this result.

Table 2. Germination enrichment techniques.

	Type	Optimal condition	GABA content	Growth multiple	Reference
Germination	Brown rice	Soak for 5.76 h; germinate at 35 ℃ for 40 h	48.2 mg/100 g	2.8	[89]
	Soy	Soak for 10 h; germinate at 25 ℃ for 3 d (protect from light)	151.0 mg/100 g	12.6	[83]
	Soybeans	Soak at 30 ℃ for 6 h; germinate at 30 ℃ for 48 h (protect from light)	51.0 mg/100 g	2.2	[38]
	Green beans	Seed:water ratio of 1:4 (g/mL); soak at 40 ℃ and pH 5.5 for 4 h; germinate for 7 h	110.4 mg/100 g	-	[84]
Germination in conjunction with other treatments	Brown rice	Soak in 50mg/mL cellulase solution for 90 min; germinate at 30 ℃ for 32 h	32.0 mg/100 g	7.5	[90]
	Tartary buckwheat	Soak in lightly acidic electrolyzed water (pH 5.83) for 12 h; germinate at 20 ℃ for 6 d	143.2 mg/100 g	138.5	[91]
	broccoli	Soaking at 25 ℃ for 4 h; germination for 12 h in light and 12 h in dark; 1.0mmol/L mannose treatment for 6 d	195.0 mg/100 g	1.3	[86]

Table 2. (*Continued*).

	Type	Optimal condition	GABA content	Growth multiple	Reference
Germination in conjunction with other treatments	Kidney beans	Salt stress (3.00g/L sodium glutamate, 5.37mmol/L $CaCl_2$) and 0.17g/L ascorbic acid treatment; germination took place for 24 h	303.6 mg/100 g	4.4	[36]
	Pumpkin seeds	Soak in mixture of 0.2% $CaCl_2$, 3.8mg/mL MSG, and 4.0mg/mL V_{B6} at 28 ℃ for 6 h; germinate at 30 ℃ for 61.6 h	2679.0 mg/100 g	5.4	[92]
Germination combined with hypoxia treatment	Brown rice	30% moisture content; germination at 30 ℃ for 48 h; aeration every 4 h	39.2 mg/100 g	1.5	[93]
	Brown rice	Soaking at 30 ℃ for 12 h; germination at 28 ℃ for 66 h; hypoxia (CO_2) treatment at 28 ℃ for 6 h	542.8 mg/100 g	5.9	[87]
Germination and freezing treatment	Black rice	Freeze at 0 ℃ for 1 h; germinate at 24 ℃ for 72 h	195.6 mg/100 g	1.5	[88]

Based on the above discussion, the level of GABA in sprouted foods depends on their variety, germination conditions, and pre-treatment. The germination process involves factors related to stress-related conditions, such as water stress, hypoxia, reduced cytosolic pH, and cold stress treatment. Adjusting these conditions can activate the two pathways of GABA enrichment to varying degrees, namely the GABA shunt pathway and the polyamine degradation pathway[94,95]. However, germination enrichment technology has certain limitations and is mainly applicable to legumes and cereal seeds.

3.2. Microbial fermentation method

In addition to plant sources, GABA intake can be supplemented by consuming dairy products and fermented foods. Most of the GABA-producing strains used in previous studies were isolated from traditional fermented foods, such as cheese, kimchi, yogurt, and fermented soybeans (as shown in **Table 3**).

GABA is mainly produced by *Bacillus*-like bacteria, which are the largest group of GABA producers, including *Lactobacillus shortum*[96–98], *Lactobacillus fermentum*[99], and *Lactobacillus plantarum*[100], etc. Wu et al.[101] found that *Lactobacillus brevis* RK03, isolated from fish, demonstrated the highest GABA-producing capacity, with a maximum GABA yield of 62.5 g/L. Among 94 *Lactobacillus* strains isolated from artisanal Mexican cheeses by Santos-Espinosa et al.[102], two *Lactobacillus* strains, L-571 and L-572, had the highest GABA content in fermented milk, which was 7.5–20.5 times higher than those of the other strains. Moreover, under an optimal fermentation condition (37 ℃, 109CFU/mL colony concentration, 3g/L Glu, and 10 μM pyridoxal 5-phosphate), the GABA production of L-571 and L-572 increased by 10 and 1.6 times, respectively. Surprisingly, the appearance and nutritional properties of the food products were significantly improved during the GABA fermentation enrichment process. For example, after 24 h of fermentation, *Lactobacillus* short-cycled TISTR 860 could increase the GABA content of rice flour to 21.8 mg/100 g, and the tensile strength and elasticity of rice flour significantly improved[103]. Currently, the fermentation enrichment technique is mainly used in liquid (milk and some fruit juices) and semi-solid foods (cheese) to increase GABA content. The desired GABA enrichment is achieved through strain screening and fermentation process optimization, including strain, substrate, active factor, temperature, and pH. The enrichment principle of microbial fermentation is that microorganisms with a high GAD activity can catalyze the synthesis of GABA from Glu during the shunt metabolism of GABA[104].

Table 3. Microbial fermentation technology.

Strain	Strain source	Culture conditions	GABA content	Growth multiple	References
Lactobacillus brevis RK03	Saltwater fish	Cultivate with optimized broth formula (1% glucose, 2.5% yeast extract and 2 ppm of $CaCO_3$, manganese sulfate, and Tween 80, as well as 10μM pyridoxal phosphate), then add 650mM MSG for fermentation for 88 h	62.5 g/L	-	[105]
Lactobacillus brevis CGMCC1306	Traditional fermented products	Ferment in MRS medium at 35 ℃ for 72 h	104.4 g/L	-	[106]
Lactobacillus brevis A7/*Lactobacillus farnii* A11	Italian yeast	9.0 log CFU/mL, ferment at 30 ℃ for 6 h	3.9 mg/100 g	4.9	[107]
Lactobacillus brevis TISTR 860	Sauerkraut	9.0 log CFU/mL, pH 4.5, 2% MSG fermentation for 24 h	21.8 mg/100 g	-	[103]
Lactobacillus fermentum HP3	Thai fermented food	PLP of 0 μM, pH of 6.5, and temperature of 40 ℃	2.4 g/L	9.4	[99]
Lactobacillus fermentum YS2	Chinese pickled vegetables	Ferment in 100mL substrate solution (80mM MSG, 0.2mM pyridoxal 5-phosphate, and 0.2M sodium acetate buffer) at pH 4.5 and incubate at 40 ℃ for 100 min	5.2 g/L	-	[108]
Lactobacillus plantarum KB1253	Japanese pickle	pH 4.0, 20° Bx, 35 ℃, ferment for 24 h	41.0 mM	2.0	[109]
Lactobacillus plantarum HU-C2W	Chinese pickle	7.0 log CFU/mL, ferment at 37 ℃ for 40 h	1.3 g/L	1.4	[110]
Lactobacillus plantarum H64	Hops	7.0 log CFU/mL, 30% wheat bran, ferment at 30 ℃ for 24 h	14.8 mg/100 g	5.9	[111]
Lactococcus lactis L-571 or L-572	Artisan Mexican cheese	109 CFU/mL, 3g/L Glu, 100μM pyridoxal-5-phosphate, ferment at 37 ℃ for 48 h	1.2 g/L	13.4	[102]
Bacillus cereus KBC	-	Temperature of 40 ℃, pH of 7, and MSG of 5 g/L	3.4 g/L	7.4	[112]

3.3. Emerging enrichment technologies

Nowadays, in order to satisfy consumers' pursuit of nutritious, healthy, and safe food, various emerging technologies are gradually being widely used in food processing, including high-pressure (HP) processing, ultrasonic (US) treatment, pulsed-light (PL) processing, and vacuum impregnation. These technologies allow for greater retention of nutrients and the maintenance of desirable organoleptic properties. Currently, these techniques are being used to increase the GABA content in natural foods.

3.3.1. High-pressure treatment

HP treatment can induce the activation or inactivation of intrinsic enzymes, which may lead to a decrease or increase in metabolite content and concentration. Thus, HP treatment may induce an increase in the activity of enzymes related to the GABA enrichment pathway, thereby promoting GABA accumulation in plant tissues. In the study by Sasagawa et al.[113], GABA in brown rice increased about 3.5-fold after treatment at 200 MPa for 5 min and storage at saturated humidity at 25 ℃ for 15 h compared with those of control samples. Kim et al.[114] found that germinated brown rice treated at 50 MPa and 37 ℃ for 24 h had a GABA content of 111.4

mg/100 g. Similar results were obtained when Ueno et al.[115] investigated the accumulation of GABA in HP-treated soybean cotyledons. The accumulation of GABA in HP-treated plant tissues may be due to an increase in GAD activity. HP treatment can stimulate GAD activation by disrupting intracellular organelles or stimulating certain metabolic processes to promote the release of H^+ and lower pH[115,116]. In addition, HP treatment can disrupt cellular structures by activating cellulose hydrolases or by mechanical forces to accelerate the mass transfer of Glu or GAD and enhance the interaction between Glu and GAD, which may increase GABA accumulation[117,118].

3.3.2. Ultrasonic treatment

US treatment is one of the sustainable, green, and emerging technologies that is increasingly used in food processing, especially in tissue homogenization, extraction of active compounds, drying, enzyme inactivation, and filtration. US treatment may be a potential method to enrich GABA. Ding et al.[119] found that the GABA content of red rice after germination increased after US treatment. This study found that metabolites related to the GABA shunt, such as Glu, alanine, and succinic acid, increased in US-treated germinated red rice. US treatment may promote the energy metabolism of germinated red rice by increasing GAD activity, thereby promoting the accumulation of GABA. Similar principles are also reflected in the study by Yang et al.[120]. They use US treatment to treat soybean seeds and then germinate them. The results showed that the GABA contents of the US-treated samples were higher than those of the untreated samples. US treatment before seed germination can activate the GAD in seeds. In addition, the principle of US treatment to enrich GABA has been deeply studied in the study by Sun et al.[121]. In this study, the activities of GAD, DAO, and AMADH in US-treated coffee leaves significantly ($p < 0.05$) increased to 3.7 times, 1.5 times, and 2.2 times, respectively, compared with those of the untreated group. In addition, after US treatment, PAO activity slightly increased ($p > 0.05$), while GABA-T activity significantly decreased ($p < 0.05$). This study showed that US treatment increased the permeability of coffee leaf cell membranes, thereby accelerating the migration of sodium glutamate into cells and increasing the concentration of intracellular substrates. Secondly, US treatment affected the activity of enzymes (GAD, GABA-T, DAO, PAO, and AMADH) involved in GABA biosynthesis and metabolism, thereby increasing the accumulation of GABA by 4.6 times.

3.3.3. Pulsed-light treatment

PL treatment is considered a very promising non-thermal technology. It employs a broad spectrum of high-intensity light (typically 100–1100 nm) covering the ultraviolet, visible, and near-infrared wavelength ranges and is applied in very short pulses. Appropriate PL treatments can also maintain or enhance the activity of certain enzymes in plants. Studies have confirmed that specific doses of PL irradiation can enhance the activity of endogenous enzymes in brown rice, including GAD, α-amylase, and protease, which may be beneficial in increasing the levels of certain nutrients. There are limited studies on GABA enrichment using PL. Zhang et al.[122] conducted a one-way test with pulsed bright light intensity, number of irradiations, and irradiation distance as the response factors and γ-aminobutyric acid enrichment as the response value. The optimal process for γ-aminobutyric acid enrichment by pulsed intense light in germinating brown rice was at light intensity of 0.45 kJ, number of irradiations of 395 times, and irradiation distance of 9.0 cm, where the γ-aminobutyric acid content of germinating brown rice reached 170.1 mg/100 g. Wang et al.[123] investigated the effects of different single energies, the number of flashes, and the starting time of intense pulsed light (IPL) on the GAD in the germination process of brown rice. The results showed that after soaking the brown rice, the GAD vigor reached 10.8 $mg\cdot(g\cdot min)^{-1}$ after 25 h of germination at a single flash energy of 400 J and 300 flashes, which was 2.2 times higher than that of the control group. Zhang et al.[124] found that the GABA content of the PL group was higher than that of the control group at all germination stages. The GABA content of the

PL group peaked at 48.8 mg/100 g after 24 h of germination. PL treatment may have accelerated protein hydrolysis and increased Glu content and GAD activity in the PL group, thereby promoting GABA production. However, lower PL energy intensities could not effectively penetrate the cell membrane of the organisms and had limited activation of endogenous enzyme activities in the brown rice. Excessively high PL energy intensities can lead to instantaneous high temperatures inside the brown rice, resulting in partial GABA decomposition.

3.3.4. Vacuum and low-pressure plasma treatments

Vacuum treatment and low-pressure plasma treatment also utilize hypoxia to increase GABA content, as shown in **Table 4**. Wang et al.[125] treated rice grains in a vacuum for 10 h at the beginning of germination, and the highest GABA content of 210.1 mg/100 g dry basis was achieved in germinated rice grains, which increased by 50.4% compared with that of germinated rice grains that were not treated in a vacuum. Jiang et al.[126] investigated the process conditions for enriching GABA in germinated peas in a vacuum treatment. The results showed that the GABA content in peas was as high as 210.7 mg/100 g, which was 2.8 times higher than the GABA content of the raw material and 1.7 times higher than that of germinated peas under the condition of 10 h of soaking time, 8 h of vacuum time, 35 ℃ germination temperature, and 0–5 h of vacuum period. Vacuum treatment is essentially a low-oxygen stress treatment; in the case of low oxygen, lactic acid in the plant will increase sharply, and so the hydrogen ion concentration in plant tissues will increase, which in turn can promote the synthesis of GABA. However, the vacuum time should not be too long; otherwise, it leads to a decrease in GABA content due to exceeding the tolerance limit of the pea tissues.

Zargarchi and Saremnezhad[127] found that increasing the plasma power level could enhance GABA enrichment. Seeds treated with 100W and 50W plasma had GABA contents 10.8 and 8.6 times higher than that of the control, respectively. Chen et al.[128] investigated the effect of low-pressure plasma on the GABA content of Japonica rice at different voltage levels, and only 3kV low-pressure plasma treatment for 10 min could significantly increase the germination of GABA content. Treatment for 10 min could significantly increase the GABA content of germinated seeds, which was about 1.5 times higher than that of unexposed samples. The early stage of water absorption by dry seed immersion is the critical period for seed germination. The extent of water uptake depends on three factors: (1) the composition of the seed, (2) the permeability of the seed coat, and (3) the availability of water[128]. Chen et al.[129] found that plasma treatment led to the etching of the surface of brown rice, which made water more readily available for uptake by rice kernels. This resulted in higher germination rates and, thus, increased GABA enrichment.

Table 4. Emerging enrichment technologies.

	Type	Optimal condition	GABA content	Growth multiple	Reference
High-pressure processing	Brown rice	200 MPa for 5 min	21.0 mg/100 g	3.5	[113]
	Brown rice	200 MPa for 10 min at 25 ℃	1.73 μmol/g	1.2	[130]
	Sprouted brown rice	50 MPa for 24 h at 37 ℃	111.4 mg/100 g	3.9	[114]
Ultrasonic treatment	Sprouted red rice	25 kHz, 16 W/L for 5 min.	75.8 mg/100 g	1.7	[119]
	Soybean seeds	300 W for 30 min at 25 ℃	119.3 mg/100 g	1.4	[120]
	Coffee leaves	20/40 kHz and 150 W for 5 min at 28 ℃	-	4.6	[121]
Pulsed light treatment	Sprouted brown rice	Pulsed light energy 0.50 of J/cm^2, irradiation distance of 8 cm, and pulse count of 400 times	48.8 mg/100 g	6.5	[124]
	Sprouted brown rice	Pulsed light energy of 0.45 kJ, distance of 9.0 cm, and number of exposures of 395	170.1 mg/100 g	-	[122]

Table 4. (*Continued*).

	Type	Optimal condition	GABA content	Growth multiple	Reference
Low pressure plasma treatment	Rice	Pre-treatment with low-pressure plasma of 100 W for 5 min; immersion at 25 °C for 48 h; sprouting at 30 °C and 90%-95% RH for 48 h	16.0 mg/100 g	10.8	[127]
	Brown rice	3kV low-pressure plasma treatment for 10 min	28.0 mg/100 g	1.5	[128]
Vacuum treatment	Sprouted peas	Soaking time of 10 h, vacuum time of 8 h, germination temperature of 35 °C, and vacuum period of 0–5 h.	210.7 mg/100 g	1.7	[126]
	Sprouted rice	Vacuum treatment for 10 h	210.1 mg/100 g	1.5	[125]

4. Health benefits of GABA-rich foods

GABA has become a popular bioactive compound in the food industry. Therefore, GABA-rich foods have many health benefits, which include hypoglycemic, hypotensive, neuroprotective, antidepressant, sleep-improving, antioxidant, and anti-inflammatory effects, as shown in **Figure 3**. Mung beans fermented by *Rhizopus* sp.[131] and yogurt fermented by *Streptococcus salivarius*[132] could enhance their antihyperglycemic effects by lowering blood glucose, glycosylated hemoglobin, cholesterol, triglyceride, and LDL levels in diabetic mice. Intervention with GABA-rich wheat bran in rats on a high-fat diet also improved glucose homeostasis[133]. Chen et al.[134] found that GABA-rich buckwheat had hypotensive potential, with up to 87.80% inhibition of angiotensin-converting enzyme, which was 2.6 times higher than that of primal buckwheat. Nishimura et al.[135] administered 150 g of GABA-enriched buckwheat to 39 mildly hypertensive adults and 150 g of GABA-enriched rice and performed hematology at weeks 0, 4, and 8. The results showed that morning systolic blood pressure was significantly lower at weeks 6 and 8 during the intervention period and at week 1 post-intervention compared with that of placebo rice. Oral administration of 50 mg/kg body weight of GABA extract from kelp to demented mice for four weeks resulted in significant improvement in cognitive dysfunction and neurological dysfunction[5]. Li et al.[136] reported that GABA-enriched chickpea milk protected neuroendocrine PC-12 cells from $MnCl_2$-induced damage, improved cell viability, and reduced the release of lactate dehydrogenase.

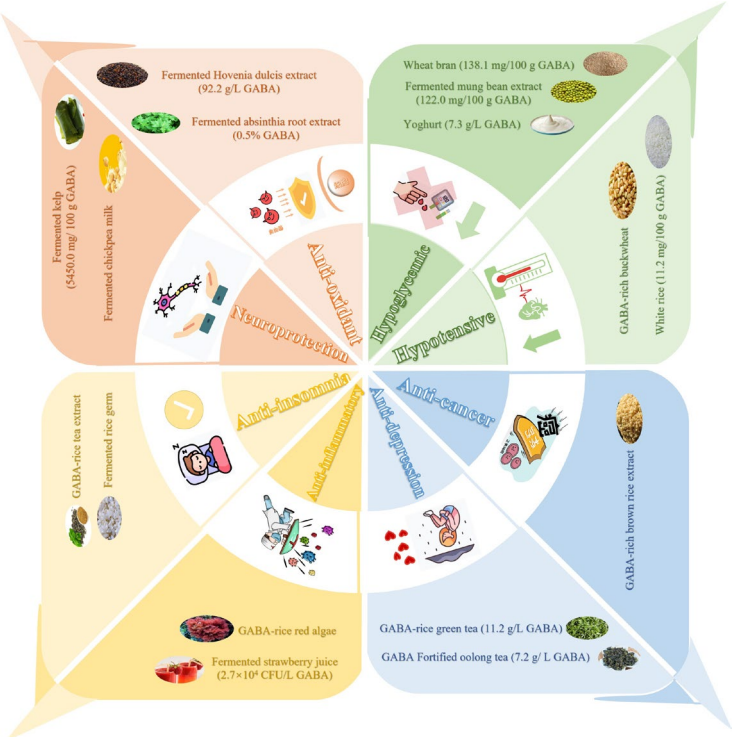

Figure 3. Health benefits of GABA-rich foods.

Consumption of GABA-rich tea has also been shown in several studies to alleviate depressive symptoms, reduce oxidative stress, and improve behavioral parameters associated with depression[137–139]. In a study by Daglia et al.[138], gavage of GABA-rich tea extract at 10 mg/kg or 20 mg/kg for one week in a PSD mouse model significantly attenuated depressive mood and reduced the levels of lipid peroxidation products in the brains of the mice. Byun et al.[140] conducted a randomized, double-blind trial, in which 40 patients suffering from insomnia were fed 300 mg of GABA-rich fermented rice tea per day. After four weeks, the patients' sleep latency was significantly reduced from 13.4 min to 5.7 min ($p = 0.001$) and sleep efficiency was significantly increased from 79.4% to 86.1% ($p = 0.018$). Park et al.[141] fed GABA-enriched (92.2 g/L) fermented Hovenia dulcis extract to mice for 29 days and found that sleep efficiency could significantly improve by the enhancement of the antioxidant defense system, the reduction of fatty acid oxidation, and the reduction of lipogenesis to prevent ethanol-induced liver injury in the mice. In addition, GABA-rich fermented absinthium root extract could up-regulate ethanol dehydrogenase, aldehyde dehydrogenase, and superoxide dismutase mRNA expression and dose-dependently decrease liver enzyme activities, thereby increasing alcohol metabolism and exhibiting antioxidant and anti-inflammatory effects, which induces liver protection from alcohol-induced injury. GABA-rich fermented strawberry juice exerted anti-inflammatory effects by inhibiting pro-inflammatory cytokines and modulating immune responses in RAW 264.7 cells of Balb/c mice[142]. GABA-rich red algae significantly inhibited IL-1α release and NGF secretion, suppressed neuroinflammatory mediators, and exhibited significant neurorelaxant activity[143].

5. Conclusion

In summary, GABA is widely distributed but naturally low in various natural foods. GABA can be effectively enriched in foods by bioconcentration techniques, including heat and humidity treatment, heat and cold stress treatments, hypoxia stress treatment, as well as germination and microbial fermentation, but it is affected by many factors, such as the species of the enriched vector (genotype), the process condition of the treatment, and the environment in which it lives. GABA-enriched foods have also been shown to possess numerous health benefits, including hypoglycemic, hypotensive, neuroprotective, antidepressant, insomnia-improving, antioxidant, and anti-inflammatory effects. Although a great deal of research has been conducted on GABA enrichment techniques, there are still issues that need to be improved: (1) food carriers that are easy to enrich with GABA should be selected for cultivation; (2) considering that microbial fermentation possesses a better enrichment effect than plant stress, in the future, emphasis should be placed on screening excellent strains with high GABA production and expanding production; (3) more efforts should be made to emphasize the stability of GABA during storage and to develop innovative technologies to enhance GABA in traditional foods or minimize processing losses; and (4) with the application of many emerging technologies in the food industry, more emerging technologies should be considered in the future to combine with GABA enrichment to explore the effect of food processing on the GABA enrichment of foods.

Author contributions

Investigation, data curation and writing—original draft preparation, YL; supervision, LZ and KW; review and edit, resources and project administration, XL and ZH. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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