

## **GABA-Enriched Functional Foods Aiding in Health and Disease Management**

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### **ABSTRACT**

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Gamma-Aminobutyric acid (GABA) plays a major role in human health. Since it is found throughout the body, its effects are widespread, and numerous health benefits of GABA have been found, including decreasing symptoms of anxiety, depression and schizophrenia. Despite the fact that only small amounts of GABA pass through the blood-brain barrier, orally ingested GABA seems to bring many health benefits. Lactic acid bacteria (LAB) have proven effective as a food additive using fermentation to enhance foods with GABA. Many food media have been used successfully with LAB to produce high levels of GABA, including kimchi, brown rice, the Asian adzuki bean, and many milk products, including cheese. These foods are made with a purpose of a specific health benefit or to treat disease and are called functional foods. GABA-enriched functional foods have been shown to benefit health, including lowering hypertension, aiding the digestive tract, decreasing the effects of chronic ethanol use, acting against alcohol hepatotoxicity, and improving longterm memory. This relatively new area of research requires much more study to explore the best functional food options for GABA, to further learn the roles of GABA in the body, and to explore GABA's various health benefits and diseases it might treat.

### INTRODUCTION

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Gamma-aminobutyric acid (GABA), a four-carbon, non-protein amino acid, is produced by a vast diversity of prokaryotic and eukaryotic organisms (Liao, 2013). It plays various physiological roles in humans and animals, including being known as a neurotransmitter in neural inhibition (Crayan and Kaupmann, 2005). In addition, GABA receptors are found throughout the human body, including the brain, the central nervous system, the lung, liver, gastrointestinal tract, sperm, testes, mammary gland, and hepatic tumor cells (Watanabe et al., 2002, Chapman et al., 1993, He et al., 2001, Opolski et al., 2000, Kleinrok et al., 1998, Minuk, 2000, Davenger et al., 1989, Fletcher et al., 2001). The physiological presence of GABA receptors has increased research interest, and studies show that GABA may have significant health effects. Since GABA is only found in low levels in natural substances, much GABA research focuses on finding new ways to produce products high in GABA.

Although studies have highlighted the possible benefits GABA may bring, extra GABA in the system will prove fruitless unless it can reach the areas needed to have an effect. For example, except for small amounts of GABA that can cross the blood-brain barrier into the brain through the pituitary gland or out of the brain when GABA levels are too high (Kakee et al., 2001), the brain typically makes the GABA needed within it. Oral GABA have been found to elevate growth hormone levels, produced in the pituitary gland (Powers et al., 2008), and Anderson and Mitchell (1986) found GABA-A and GABA-B binding sites in the rat pituitary gland. In addition, oral administration of GABA increases growth hormone concentrations by about 400%, from approximately 2  $\mu\text{g/L}$  to nearly 8  $\mu\text{g/L}$ , and growth hormones are produced by the pituitary gland (Powers et al., 2008). Thus, although some orally ingested GABA reaches the brain via the pituitary gland, the amounts may not be enough to produce the desired effects in the brain.

Because the blood-brain barrier limits GABA from crossing into the brain and because of GABA's

importance as a neurotransmitter and its potential benefits as a health supplement, pharmaceutical manufacturers and chemists have designed GABA-like substances (supplements and prescription drugs) that can cross the blood-brain barrier and mimic the functions of GABA in the brain (Lapin, 2001). For example, the GABA analogue Phenibut, or beta-phenyl-gamma-aminobutyric acid HCl, can cross the blood-brain barrier because a 6-carbon ring is added to the GABA, enabling it to cross the blood-brain barrier and still appropriately act on GABA receptors; however, Phenibut is not approved for use in the US or Europe as a pharmaceutical (Lapin, 2001). Phenibut not only acts as an anxiolytic but can also enhance cognition (Lapin, 2001). Picamilon, or nicotinoyl-GABA, had niacin added to the GABA molecule to allow this GABA analogue to cross the blood-brain barrier. With picamilon, once it crosses the blood-brain barrier, pure GABA results, due to the cleaving of the niacin molecule (Lapin, 2001). Thus, the GABA in the brain resulting from picamilon is identical to the GABA produced inside the brain (Lapin, 2001).

Interestingly, although Phenibut and picamilon penetrate the blood-brain barrier better than GABA, they do not lead to significantly stronger pharmacological effects (Lapin, 2001). In addition, Phenibut does not carry the anticonvulsant effects that GABA does (Lapin, 2001); and GABA can likely benefit the body without crossing the blood-brain barrier, targeting GABA receptor sites throughout the body. Thus, despite an inability to cross the blood-brain barrier, increased GABA within the body may still carry the desired health benefits because of the pervasiveness of GABA receptors. This shows a need for ways to increase GABA in the body.

Various strains of lactic acid bacteria (LAB) have been found to effectively increase the growth of GABA in various media. Much of the research in this area has centered on producing food products with additional ingredients to expand the food's functions, which typically includes adding a specific

health benefit or focusing on preventing a specific disease. The food industry refers to these products as functional foods. Functional foods have increasingly used LAB to significantly enhance GABA content, and GABA-enhanced products have also been found to have various health benefits (Kim, 2012). The beneficial physiological effects that GABA can have on the body highlight that it may be an important area of study to find the most effective methods of producing foods with high GABA content. Various strains of bacteria have proven useful in synthesizing GABA in many media. Many studies focus on finding the ideal conditions for maximum GABA production using LAB, and many of these products have been shown to have positive health effects.

### **BACTERIAL DEVELOPMENT OF GABA**

Bacteria can produce elevated levels of GABA in different types of food. Many strains of lactic acid bacteria (LAB) produce GABA through fermentation of food products (Thwe et al., 2011). The results of these findings offer potential alternatives to take advantage of GABA's health benefits through GABA-enriched foods. While research continually finds new foods ideal for the GABA-enrichment process, several food products are already marketed as being GABA-enriched, including anaerobically treated tea leaves (Tsushida et al., 1987), water-soaked rice germs (Saikusa et al., 1994), red mold rice (Kono and Himeno, 2000), fermented soy beans (Aoki et al., 2003), and dairy and fermented milk products, such as yogurt (Park and Oh, 2007, Hayakawa et al., 2004).

Knowing this basic background offers a potential solution. Humans sometimes may benefit from additional GABA in their bodies; thus, increased GABA in their food, supplements or medicine could prove useful. However, since fresh food typically only contains low levels of GABA, bacteria can be used to synthesize GABA by using GAD to metabolize glutamate. Research has found many ways to use bacteria to increase GABA in functional food products to make the health benefits of GABA more

widely available.

Bacterial GABA production comes through various GAD enzymes which are only found in bacteria. For example, *Escherichia coli*, a bacteria found in high concentrations in the GI tract, have different GADs, including GADX, GADW, GADB, and GADC, that can increase the GABA production within *E. coli* (Tramonti et al., 2008, Vo et al., 2011). In addition, *Lactobacillus* actively produces GABA (Fan et al., 2011) and is very active in many foods that are readily consumed, (Table 1). Other microorganisms also produce elevated levels of GABA in common food products (Table 1).

Since the health benefits of GABA-synthesized foods have become better known, their importance in the food industry has grown (Komatsuzaki et al., 2005). While some LAB strains produce GABA, others do not (Nomura et al., 1999). Thus, it is important to study further to isolate those LAB strains which do produce GABA and expand their application to a greater number of fermented foods (Tung et al., 2011). Below, a number of examples are given where fermentation was used with a LAB to increase the GABA already present in a food item.

Kimchi samples have been used with LAB to help synthesize GABA (Cho et al., 2011, Kim and Kim, 2012). A study by Kim and Kim (2012) found five different species of GABA-producing bacteria within their kimchi samples; these included *Lactobacillus plantarum*, *Lactobacillus brevis*, *Leuconostoc mesenteroides*, *Leuconostoc tactis*, and *Weisella viridescens*.

It is important to note that only 30% of the isolated kimchi samples showed a presence of LAB, and these were from 11 of 20 kimchi samples (Kim and Kim, 2012). Thus, though some kimchi may have the bacteria present to synthesize GABA, this finding cannot be generalized. Another study found that

GABA amounts were 8 times higher when using *Lactobacillus buchneri* as a starter for kimchi fermentation than without (Cho et al., 2011). Thus, GABA-synthesized kimchi presents a functional food source for GABA.

The Asian adzuki bean has also been used as a medium to use GABA-producing bacteria and fermentation. One study investigated *Lactococcus lactis* and *Lactobacillus rhamnosus*, using the adzuki bean while testing processes like immersion, germination, and cold shock before the fermentation process (Liao et al., 2013). Results showed a 150 times increase of GABA produced by using the cold shock treatment on the adzuki beans compared to non-treated adzuki beans (Liao et al., 2013). For the most optimal production of GABA, the cold-shocked adzuki beans are fermented for 24 hours at 30°C (Liao et al., 2013). A carbon source of sucrose from the bean and nitrogen sources, including pancreatic protein, yeast extract, peptone and skim milk powder, also helped to produce a higher GABA content with the mixed strains *L. lactis* and *L. rhamnosus* (Liao et al., 2013). This presents a useful way to produce high GABA levels in a functional food source using organic nitrogen sources.

Black raspberry juice, along with *L. brevis*, was used as a medium for fermentation to produce GABA (Kim et al., 2008). Various temperatures and pH's were used to find the most effective method of producing high levels of GABA (Kim et al., 2008). After 15 days of fermentation, even if the number of bacteria decreased, the mix of juice and *L. brevis* continually produced GABA. Keeping the medium at 30°C typically showed a higher yield of GABA, which reached its highest levels on the 12<sup>th</sup> day of fermentation (Kim et al., 2008). The results show that LAB can be used to enrich black raspberry juice with GABA, presenting yet another way to enrich a diet with GABA.

**Table 1.** GABA production is listed by amount of GABA produced by respected bacteria in units of mg/kg or mg/l, depending on how original reporting was published. All listed bacteria will produce GABA naturally, outside of the isolation source.

Microorganism	Isolation in	GABA Produced
Streptomyces bacillaris strain Y11	Tea	2.4 mg/kg (Jeng et al., 2007)
Streptomyces bacillaris strain R9	Tea	2.9 mg/kg (Jeng et al., 2007)
Lactobacillus brevis PM17	Cheeses	15 mg/kg (Siragusa et al., 2007)
Lactobacillus plantarum C48	Cheeses	16 mg/kg (Siragusa et al., 2007)
Lactococcus. lactis PU1	Cheeses	36 mg/kg (Siragusa et al., 2007)
Lactobacillus. delbrueckii subsp. Bulgaricus PR1	Cheeses	63 mg/kg (Siragusa et al., 2007)
Lactobacillus paracasei PF6	Cheeses	99.9 mg/kg (Siragusa et al., 2007)
Lactobacillus sp. OPK 2-59	Kimchi	180 mg/kg (Seok, et al., 2008)
Lactococcus lactis subsp. lactis PU1	Cheeses	258.71 mg/kg (Rizzello et al., 2008)
Lactobacillus plantarum C48	Cheeses	504 mg/kg (Coda et al., 2010)
Monascus purpureus CCRC 31615	Laboratory	1493.6 mg/kg (Su et al., 2003)
Rhizopus microspores var. oligosporus IFO 32003		15000 mg/kg (Aoki et al., 2003)
Lactobacillus brevis	Paocai	15370 mg/kg (Li et al., 2008)
Rhizopus microspores var. oligosporus IFO 32002		17400 mg/kg (Aoki et al., 2003)
Monascus purpureus CMU001		28370 mg/kg (Jannoey et al., 2009)
Lactobacillus plantarum DSM19463	Cheeses	498.1 mg/l (Cagno et al., 2009)
Lactobacillus brevis IFO- 12005		1049.8 mg/l (Yokoyama et al., 2002)
Lactobacillus brevis BJ20	Kimchi	2465 mg/l (Lee et al. 2010)
Lactococcus lactis ssp. Lactis 017	Cheeses	2700 mg/l (Nomura et al., 1998)
Lactobacillus brevis	Fresh Milk	4599.2 mg/l (Huang et al., 2006)
Streptococcus salivarius subsp. Thermophilus Y2		6000 mg/l (Yang et al., 2007)
Lactococcus lactis subsp. lactis	Kimchi, yogurt	6410 mg/l (Lu et al., 2008)
Lactococcus lactis subsp. lactis	Kimchi	7200 mg/l (Lu et al., 2009)
Lactobacillus brevis GABA 100		13000 mg/l (Kim et al., 2009)
Lactobacillus brevis GABA 057		23381 mg/l (Choi et al., 2006)
Lactobacillus buchneri MS	Kimchi	25883.12 mg/l (Cho et al., 2007)
Lactobacillus paracasei NFRI 7415	Funa-sushi	31145.3 mg/l (Komatsuzaki et al., 2005)
Lactobacillus brevis NCL912	Paocai	35662 mg/l (Li et al., 2010)
Lactobacillus brevis NCL912	Paocai	103719 mg/l (Li et al., 2010)



Various types of cheese have been used as media for GABA synthesis. In one study, 440 LAB strains were isolated from 22 Italian cheeses and tested for their ability to synthesize GABA using fermentation of reconstituted skim milk (Siragasu et al., 2007). Of the 440 isolates, only 61 showed the synthesis of GABA. Twelve different species of LAB were identified using partial sequencing of the 16S rRNA gene, including the strains *Lactobacillus paracasei* PF6, *Lactobacillus delbrueckii subsp. bulgaricus* PR1, *Lactococcus lactis* PU1, *Lactobacillus plantarum* C48, and *Lactobacillus brevis* PM17 (Siragasu et al., 2007). All of these bacteria were isolated from the isolate cheeses with the highest concentrations of GABA, excepting *L. plantarum*. Under stimulated gastrointestinal conditions, three of the lactobacillus strains survived and continued to synthesize GABA (Siragasu et al., 2007). Four of the bacterial strains (*L. paracasei* PF6, *L. delbrueckii subsp. bulgaricus* PR1, *L. lactis* PU1, and *L. plantarum* C48) contained glutamic-acid decarboxylase (GAD) DNA fragments, which were isolated using primers centered on two GAD regions that are highly conserved (Siragasu et al., 2007). The presence of GAD DNA fragments suggests an increased ability to produce GABA, since GAD must be present to produce GABA. In addition, three of the four strains, excluding *L. lactis* PU1, survived simulated gastrointestinal conditions and continued to synthesize GABA in these conditions (Siragasu et al., 2007). These results showed potential for producing GABA enriched dairy products through cheese-related lactobacillus strains. They also show an even more important possibility of these media continuing with GABA production once ingested, further improving the health benefits of a GABA-enriched product.

*L. plantarum* NTU 102 (fermented skim milk) was used to synthesize GABA. As discussed earlier, GAD catalyzes GABA synthesis (Tung et al., 2011). Thus, because different strains of LAB have various abilities to produce GABA and respond differently to medium compositions, maximizing production through ideal conditions plays a role in GABA production (Tung et al., 2011). Knowing

GAD's biochemical properties helps to optimize conditions. In addition, GABA fermentation's optimal conditions for diverse LAB strains will vary (Tung et al., 2011). For *L. plantarum* NTU 102 optimized conditions included skim milk as a carbon source, a specific glutamate concentration (0.6%-1%), a specific culture temperature (37°C), with a 24 hour incubation period to allow time for bacterial growth and cell biomass production (Tung et al., 2011). In addition, a lower pH present after the 24 hour incubation time and the death of the bacteria after the 24 hours, may have assisted in GABA synthesis (Tung et al., 2011). The researchers hypothesized that the bacteria's death after 24 hours of incubation released GAD, thus greatly increasing the production of GABA (Tung et al., 2011). Successful production of GABA, as in this study, has become increasingly important as the food industry has higher demand for such products (Tung et al., 2011).

Many milk products can be used in tandem with LAB to synthesize GABA. Another milk product that has been successfully GABA-enriched is yogurt using the LAB *L. brevis* and germinated soybean extract (Park and Oh, 2007). The yield of GABA with the *L. brevis* present throughout the fermentation process compared to the conventional fermentation process, without *L. brevis*, was significantly higher (Park and Oh, 2007). *L. brevis* has specifically been found to produce high levels of GABA in dairy products (Hou et al., 2013). This bacterial strain has increased GABA levels in dairy products faster than other strains (Hou et al., 2013). One study using skim milk culture to enhance GABA synthesis included nine mixed-strain starters (Nomura et al., 1998). *Lactococcus lactis ssp lactis* was isolated as the GABA-producing bacterium, and GAD activity was detected between pH levels of 4.5 and 5.0, with the optimal pH for GAD activity being 4.7 (Nomura et al., 1998). No GAD activity was detected with a pH over 5.5, and the enzyme became completely inactive when heat treated at 100°C for one minute (Nomura et al., 1998). This same strain was used to prepare cheeses, where the lower the pH level, the higher the GABA production (Nomura et al., 1998). In this study, it

was concluded that GABA was produced by the cheese starters during ripening (Nomura et al., 1998). Thus, a number of different dairy products can be successfully used as GABA-enriched functional foods.

Numerous foods can act as a medium for bacteria-produced GABA, including using *L.brevis* IFO-12005 in rice shochu distillery lees (kome shochu kasu) as an economical process for GABA production (Yokoyama et al., 2002). In addition, GABA production increased using a high concentration of glutamate in wheat germ (Takigawa 2009). Another example of a GABA-enhanced functional food item is sugarcane-fermented lactic acid beverages, which, for optimum conditions, includes sugar cane juice (30%) and skim milk (10%) with a fermentation temperature over 30°C, with a 48-72 hour fermentation time (Hirose et al., 2008). Mochi barley grains have also shown a high yield of GABA production capability, when combined with a glutamic acid solution and with pyridoxal phosphate removed (Watanabe et al., 2012). Fermented fish products also act as an ideal medium for GABA synthesis using LAB. The bacteria *Lactobacillus farcimini* D323 proved the most effective LAB strain with fermented fishery products and boiled rice (Thwe et al., 2011), which offers another functional use for GABA-synthesized food. Thus, the functional food products available for using LAB for GABA synthesis keep growing as research in this area continues.

### **PHYSIOLOGICAL BENEFITS OF GABA**

As GABA acts as a neural inhibitor, it is found in almost every site in the body, giving it greater influence on a variety of physical health aspects. Because GABA has been found to have a likely positive affect on many health factors, studies on its effects span from gastrointestinal issues to schizophrenia. Knowing how GABA works in the human body further drives this need. Although GABA's full roles and effects on the human body are not fully known, its importance in the human

body is becoming increasingly evident.

Research has shown that GABA affects hypertension in rats. Aoki et al. (2003) used rats with spontaneous hypertension to compare effects of a GABA-enriched tempeh-like fermented soybean and the effects of authentic GABA (GABA-tempeh). In both cases, the systolic blood pressure of the rats taking GABA-tempeh and natural GABA had significant systolic blood pressure decreases compared to a control group (Aoki et al., 2003). Gillis et al. (1984) found that GABA and drugs stimulating GABA receptors cause a decrease in blood pressure, while arterial pressure increases with drugs that inhibit GABA synthesis or block GABA-mediated responses.

In another example, GABA had a relaxant and anti-anxiolytic effect in humans (Abdou et al., 2006). Using 13 subjects, Abdou et al. (2006) obtained electroencephalograms (EEG) after each of three tests: orally intaking only water, GABA, or L-theanine. Electroencephalograms showed that after 60 minutes of administration, the intake of GABA significantly increased alpha waves and decreased beta waves when compared to water or L-theanine (Abdou et al., 2006). These findings show that GABA induced relaxation and reduced anxiety (Abdou et al., 2006). Abdou et al. (2006) also found that administering GABA enhanced immunity under stressful conditions. To complete this part of the study, the researchers divided eight subjects into two groups, one group orally received placebos and the other GABA (Abdou et al., 2006). Subjects crossed a suspended bridge as a stressful stimulus, and researchers tested immunoglobulin A (IgA) levels in the subjects' saliva while crossing the bridge (Abdou et al., 2006). Abdou et al. (2006) found significantly higher IgA levels in the GABA group than the IgA levels in the placebo group. These findings show that GABA could be used to induce relaxation, diminish anxiety, and enhance immunity under stressful conditions (Abdou et al., 2006).

Although all of the neurobiological mechanisms underlying anxiety are not fully known or understood, human brain imaging shows that dysfunction in the amygdala, anterior cingulate cortex, hippocampus and medial prefrontal cortex may be responsible (Cannistraro and Rauch, 2003). Typical pharmacological treatment of anxiety disorders includes either targeting GABA by using benzodiazepines or serotonin (5-HT) systems using receptor agonists for 5-HT<sub>1A</sub>, a serotonin receptor, or using SSRIs (selective serotonin reuptake inhibitors) (Nemeroff, 2003). However, the negative side-effects of benzodiazepines (tolerance, sedation, cognitive impairments, and ethanol interactions) and the slow onset of 5-HT receptor ligands action bring major drawbacks to the current treatment approaches (Nemeroff, 2003).

The crucial overall role of GABA-mediated neurotransmission in regards to GABA-A receptors in anxiety has been known for some time (Cryan and Kaupmann, 2005). Yet, the specific role of GABA-B receptors' influence in anxiety has been unknown until a recent study focusing on the GABA-B receptors in mice showing that the activation of GABA-B receptors may reduce anxiety (Millan, 2003, Cryan and Kaupmann, 2005). Baclofen, which is not a benzodiazepine, has reversed anxiety effects in rats or mice in alcohol withdrawal (Andrews and File, 1993, File, 1991, File et al., 1992), post-traumatic stress (Drake et al., 2003), panic disorder. (Breslow et al., 1989) and spinal cord lesions (Hinderer, 1990). Positive modulators of GABA-B, such as GS39783 and CGP56433A, may also present anxiety treatments without the side effects present with benzodiazepines typically used to treat anxiety, although further studies are needed (Cryan and Kaupmann, 2005).

Although antidepressant strategies have often primarily targeted monoamines (Frazer, 1997), research evidence supports that GABA system dysfunction also links to depression (Krystal et al., 2002, Brambilla et al., 2003). For example, compared with controls, unipolar depressed patients have lower

GABA concentration in their plasma and cerebrospinal fluid (Brambilla et al., 2003). In addition, patients treated with SSRIs or electroconvulsive-shock therapy have higher levels of GABA in their occipital cortex after treatments (Sanacora et al., 2002, Sanacora et al., 2004). Even so, the exact role that GABA-B receptors play in influencing depression is unclear (Cryan and Kaupmann, 2005). GABA-B receptor antagonists have been the main body of study with GABA's connection with depression (Cryan and Kaupmann, 2005).

Molecular interaction occurs between 5-HT (serotonin) and GABA-B receptor sites. Serrats et al. (2003) showed that over 95% of the cell bodies with 5-HT-immunoreactivity also have GABA-B receptors. Yet, the exact nature of the interactions is unknown and must be studied further. However, advances in this area have shown GABA-B receptors to be a possible target for pharmaceutical treatment of anxiety and depression (Cryan and Kaupmann, 2005). Gu and An (2011) found depression-like behavior in rodents during acute forced swim stress in the orbital frontal cortex (OFC). They also observed a marked decrease in Kalirin-7 expression and the basal dendritic spine density of layer V pyramidal neurons (Gu and An, 2011). Orally administering GABA reversed all of these changes, which were inhibited by a GABA-B receptor antagonist, CGP35348 (Gu and An, 2011). Thus, this study shows that GABA can have an anti-depression effect in the OFC, with a GABA-B mediation (Gu and An, 2011).

GABA has been shown to help with sleeplessness due to problems in inhibitory processes (Gottesmann, 2002). Since GABA acts as the primary inhibitory neurotransmitter throughout the body, its role in sleep has become well-known (Gottesmann, 2002). When stimulated, the current known GABA receptors (GABA-A, GABA-B, GABA-C) have similar hypnotic effects (Gottesmann, 2002). While GABA antagonists appear to promote waking, agonists increase sleep (Gottesmann, 2002).

Insomnia treatments currently focus on GABA-A receptor modulators, with GABA-A alpha 1 receptor subtypes thought to be responsible for the sedative effects (Nutt, 2010). Nitz and Siegel (1996) found an increase in GABA during slow-wave sleep in the posterior hypothalamus. In addition, slow-wave sleep was found to extend with a microinjection of muscimol, a GABA-A receptor agonist (Nitz and Siegel, 1996).

Patients with schizophrenia have been shown to have prefrontal cortical deficits in GABA signaling, and the limbic system and cerebellum have also been found to have GABA-related deficiencies in patients with schizophrenia (Wong et al., 2003, Yager, 2008). Yu et al. (2013) found that GABA transporter 1 (GAT1) knockout (KO) mice, with elevated ambient GABA, display positive, negative and cognitive symptoms of schizophrenia. Using a GABA-A receptor antagonist picrotoxin, the behavioral defects associated with schizophrenia in the GAT1 KO mice significantly decreased (Yu et al., 2013). This study suggests that elevated ambient GABA may have a critical role in the pathogenesis of schizophrenia (Yu et al. 2013).

GABA has also been used to enhance antipsychotic medication to treat schizophrenia (BioLineRx Ltd., 2008). BL-1020, an oral GABA-enhanced antipsychotic drug in clinical trials, can be taken orally and successfully decreases psychotic symptoms without the negative side-effects (changes in body weight, extrapyramidal (motor) symptoms) typically present (BioLineRx Ltd., 2008). Clinical trials treated a group of patients with treatment resistant schizophrenia for six weeks with BL-1020 with statistically significant results and minimal side-effects (Worldwide Biotech, 2007). The severity of patients' symptoms was measured using the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) scores, both measures widely recognized to determine the severity of schizophrenia (World Biotech, 2007). Scores for the PANSS significantly improved with  $p < 0.001$ , and

CGI scores after treatment compared to baseline showed that 92.35% of patients improved in at least one area of symptoms by the end of the study (World Biotech, 2007). No test results, including ECGs, laboratory results, vital signs and adverse events, indicated “any systematic pattern of adverse change associated with BL-1020” (World Biotech, 2007). Thus, GABA-enhanced psycho-pharmaceuticals may gain a significant place in treating schizophrenia.

Effects of GABA seem to largely influence the health of the gastrointestinal (GI) system (Davanger et al., 1989, Fletcher et al., 2001, E., Hoepfner et al., 2001, Hyland and Cryan, 2010). GABA has been found in abundance throughout the GI tract, including in enteric nerves, submucosal nerve cell bodies and mucosal nerve fibers, and endocrine-like cells, suggesting that GABA acts not only as a neurotransmitter but also as an endocrine mediator in the GI tract (Hyland and Cryan, 2010). GABA has two primary receptors (ionotropic GABA-A and metabotropic GABA-B). GABA-B receptors have been found throughout the GI tract of several species, just as GABA has, including in epithelial layers and muscles, and GABA-B has been found to play a major part in health and disease within the GI tract (Hyland and Cryan, 2010).

In humans, the jejunal longitudinal muscle in the GI tract responds to GABA and baclofen to inhibit spontaneous activity (Hyland and Cryan, 2010). GABA-B receptors responds to baclofen, an agonist meant to target GABA-B receptor sites (Hyland and Cryan, 2010). For example, research shows that GABA-B agonists, namely baclofen taken orally, may be used successfully to manage reflux in patients with gastroesophageal reflux disease (Lidums et al., 2000, Ciccaglione and Marzio, 2003) in both acute and chronic cases (Ciccaglione and Marzio, 2003). However, targeting GABA-B receptors may potentially bring negative side-effects, such as drowsiness and dizziness (Lidums et al., 2000, van Herwaarden et al., 2002, Ciccaglione and Marzio, 2003). Many GI functions are regulated by



GABA-B receptor sites, making it a target to help in treating several GI disorders, although side-effects may limit the use of GABAergic medications like baclofen for therapeutic purposes (Hyland and Cryan, 2010). Thus, the use of GABA-enriched functional foods may provide an ideal therapeutic approach for GI disorders, since the typical side-effects are absent (Hyland and Cryan, 2010). Bacteria GABA-enhanced functional foods allow for easy delivery of GABA in the GI tract (Hyland and Cryan, 2010). Thus, adding GABA into the GI tract through GABA-enriched foods may prove beneficial by taking advantage of the GI functions regulated by GABA-B receptors (Hyland and Cryan, 2010).

### **INFLUENCE OF GABA-ENRICHED FOODS**

The studies discussed show that increased GABA levels seem to affect the body positively in many ways. As previously discussed, studies have led to the search for ways to increase GABA in the human diet through GABA-enriched functional foods, and many media have proved to successfully produce GABA using LABs. Yet, the importance of being able to produce higher levels of GABA in food sources means nothing without evidence of GABA having a positive health affect through the consumption of these foods. Many GABA-enriched functional foods have been tested to determine their health benefits, and a few are listed below.

Brown rice germinated under conditions favorable for GABA production successfully treated the effects of chronic ethanol abuse (Oh et al., 2003). First, consequences of chronic ethanol use were established in mice, namely the presence of enzymes indicative of liver damage and serum and hepatic lipid concentrations (Oh et al., 2003). Researchers divided the mice into three groups: the first group, the control group, received only a basic diet, the second group received the basic diet and ethanol, and the third group received the basic diet, ethanol and a brown rice extract high in GABA (Oh et al., 2003). The mice given ethanol had increased levels of serum low-density lipoprotein cholesterol

(LDL-C), liver aspartate aminotransferase, and liver alanine aminotransferase, while the mice given the ethanol and the brown rice serum did not have an increase of these (Oh et al., 2003). Oh et al. (2003) found that mice fed a high content of GABA along with ethanol avoided several alcohol-induced effects, namely increased serum low-density lipoprotein cholesterol (LDL-C), liver aspartate aminotransferase, and liver alanine aminotransferase. In addition, serum and liver high-density lipoprotein cholesterol (HDL-C) concentrations significantly increased in the mice taking the brown rice extract (Oh et al., 2003). These results provide evidence that using brown rice extract with high GABA levels may help with the recovery from the consequences of chronic alcohol use and help prevent chronic alcohol-related diseases (Oh et al., 2003).

Although the increased nutrients in germinated brown rice, used to make the brown rice extract, are many, none increase as significantly or are as abundant as GABA (Patil and Khan, 2011). GABA has been found to be ten times greater in germinated brown rice as in milled white rice (Patil and Khan, 2011). In addition, a primary reason for the popularity of germinated brown rice throughout Southeast Asia is due to its high-level content of GABA and the health benefits GABA can bring (Patil and Khan, 2011). High levels of GABA in brown rice extracts may be used to treat symptoms of chronic alcohol-related symptoms (Oh et al., 2003).

Kang et al. (2011) found a protective effect of GABA-enriched sea tangle juice against alcohol hepatotoxicity. The GABA-enriched sea tangle juice was prepared using *L. brevis* BJ20 strain through the fermentation process at 37°C (Kang et al., 2011). In this study, the effect of GABA-enriched sea tangle juice on ethanol-induced cytotoxicity in the human hepatocellular liver carcinoma cell line (HepG2) was observed (Kang et al., 2011). Although the exact protective mechanism still needs to be determined, Kang et al. (2011) found that GABA-enriched sea tangle juice prevented intracellular

glutathione depletion which ethanol consumption causes, decreased gamma-glutamyl transpeptidase activity, and suppressed the enzyme CYP2E1 expression, a major contributor to ethanol-induced oxidative stress. A control using sea tangle juice without the *L. brevis* and fermentation process did not have similar protective effects against ethanol toxicity, although it did help with cell viability against ethanol toxicity similar to the GABA-enriched medium (Kang et al., 2011). GABA-enriched sea tangle juice possessed benefits in this study that ordinary sea tangle juice did not, which shows a great benefit to GABA-enriched foods.

GABA-enhanced kimchi was found to improve long-term memory loss recovery in mice who had been given scopolamine to decrease their cognitive function (Seo et al., 2012). All mice were tested for memory loss before the test (Seo et al., 2012). Seo et al. (2012) isolated the LAB strain *Lactobacillus sakei* B2-16 from kimchi and used 12% (w/v) monosodium glutamate (MSG) to produce GABA, resulting in a 660 mM GABA in the extraction. The culture medium included 1% rice bran, 4% sugar as a carbon source, 2% yeast extract as a nitrogen source, and the 12% MSG with a 48 hours fermentation period (Seo et al., 2012). In this study, results showed that a high-dose of GABA resulted in the greatest efficacy (Seo et al., 2012). While 46.69 mg/mL GABA improved the mice's memory from 132 seconds to 48 seconds, an 85% recovery compared to the control group, lower doses of GABA enhanced the memory only 20% (Seo et al., 2012). Administration of GABA, using the GABA-enhanced extract and standard commercial GABA, also increased the number of neurites in PC-12 cells, with the greatest increase coming after the third day of cultivation (Seo et al., 2012). The study controlled for other nutrients and substances within the GABA-enhanced extract by administering these nutrients and substances without the GABA to the control group (Seo et al., 2012).

Specific research on GABA-enriched functional food products must be expanded. While more GABA-enriched functional foods are being produced, more research is needed targeting and studying specific health benefits of consuming these foods. It is particularly important to find those GABA-enhanced functional foods that bring the greatest effects, especially foods with a bacteria strain that allows GABA production to continue after ingestion. While the general effects of GABA to treat health issues has a larger base, specifically using GABA-enriched functional foods to treat these same health issues needs to be explored.

### **CONCLUSION**

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Bacteria-produced GABA can be utilized in functional food products in numerous ways, and GABA-enriched food's health benefits can be vast, although the knowledge of their breadth of specific benefits needs to be expanded. Benefits of a GABA include helping with sleeplessness, lowering anxiety symptoms, helping to alleviate depression, induce relaxation in times of stress, increase immunity, decreasing memory loss, protecting against the effects of alcohol toxicity, alleviating hypertension, decreasing symptoms of schizophrenia, and relieving GI disorders. Further research needs to be conducted on the benefits of specific GABA-enhanced functional foods, to find the most beneficial media to deliver GABA into the body and to see if the benefits continue with various media. Many questions are left to further develop why GABA has the benefits it does and what specific mechanisms are used to benefit the body's health on a molecular level given a certain GABA-enriched functional food or supplement. For example, although knowledge of the role of GABA-B receptors has expanded, much about the functions of GABA-B receptors is yet to be discovered. In addition, little information is known about GABA-C receptors and how they influence the body. Knowing more about these receptors could bring more information about why GABA and GABA-enriched foods have the positive effects that have been found. Further research is also needed on the functions of GABA

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throughout the body. Although GABA is found throughout the body, many of its functions remain unknown. This is a newer area of study, leaving much space for expansion, details and greater understanding; however, at least some benefits of GABA-enriched foods and pharmaceuticals have been established.

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