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REVIEW ARTICLE

A Brief Review on the Non-protein Amino Acid, Gamma-amino Butyric Acid (GABA): Its Production and Role in Microbes

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Abstract
Gamma-Aminobutyric acid (GABA) is a non-protein amino acid widely distributed in nature. It is produced through irreversible α-decarboxylation of glutamate by enzyme glutamate decarboxylase (GAD). GABA and GAD have been found in plants, animals, and microorganisms. GABA is distributed throughout the human body and it is involved in the regulation of cardiovascular conditions such as blood pressure and heart rate, and plays a role in the reduction of anxiety and pain. Although researchers had produced GABA by chemical method earlier it became less acceptable as it pollutes the environment. Researchers now use a more promising microbial method for the production of GABA. In the drug and food industry, demand for GABA is immense. So, large scale conversion of GABA by microbes has got much attention. So this review focuses on the isolation source, production, and functions of GABA in the microbial system. We also summarize the mechanism of action of GABA and its shunt pathway.

Introduction

Gamma-aminobutyric acid (GABA) is a non-protein amino acid and it is produced through α-decarboxylation of L-glutamic acid in a reaction catalyzed by glutamate decarboxylase (Fig. 1). Half a century ago Steward et al. [1] in 1949 had first discovered GABA in plants and later Roberts and Franklin [2] in 1950 discovered it in the mammalian brain. Roberts and Heidelbergin 1960 [3] made another great leap revealing its major role in the neurotransmission of animals. It is found predominantly in the brain where it acts as an important inhibitory neurotransmitter. GABA and its receptors are also detected in the peripheral system, endocrine, and several non-neural tissues where it plays a role in oxidative metabolism. GABA has 3 receptors alpha or A, beta or B, gamma or C which recognize and bind GABA and these receptors are located in the postsynaptic membrane. GABA-A and GABA-C receptors are ligand-gated ion channels while GABA-B receptors are G protein-coupled receptors. GABA -A receptors mediate fast synaptic transmission whereas GABA-B mediates slow synaptic transmission. Seizure, threshold, anxiety, and panic are associated with GABA -A receptors and GABA -B receptors are associated with memory, mood and pain. Although GABA -C receptors have been identified, its physiological role has not yet been recognized. There is an increase of interest in research for GABA and its receptors and studies demonstrate that GABA can have important health effects. GABA promotes the metabolism of brain cells by increasing the oxygen supply, activating cerebral blood flow and inhibits the secretion of the vasopressin by acting on the vasomotor center of the medulla oblongata. In addition to its diuretic, anti-depressive, and anti-oxidant effects, it regulates growth hormone secretion, drops the blood pressure by expanding the blood vessels [4–8]. It acts as an effective pain reliever, regulates cardiovascular function and used as medicine for stroke treatment. GABA has been known to be effective to regulate several neurological disorders such as Parkinson's disease, Huntington's chorea [9], and Alzheimer's disease. Moreover, GABA stimulates cancer cell apoptosis and has an inhibitory effect on cancer cell proliferation. In food and pharmaceuticals, it used as a bioactive component [10].

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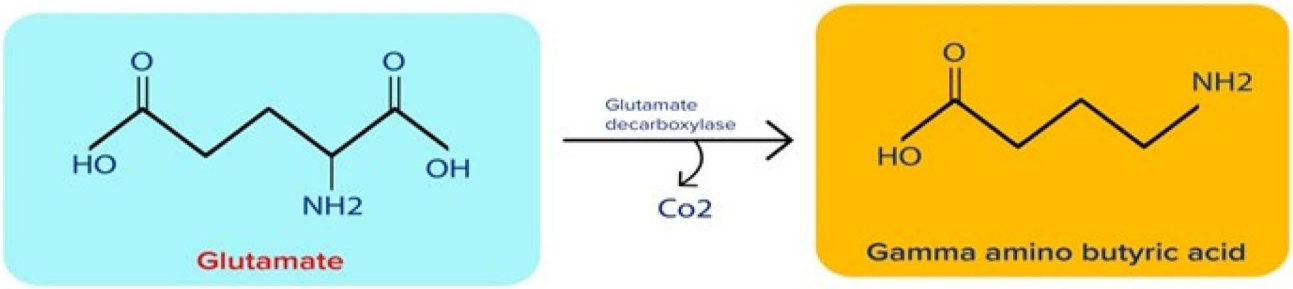

Fig. 1 Decarboxylation of glutamate to GABA by glutamate decarboxylase

Mechanism of Action of GABA

Gamma-aminobutyric acid is a neurotransmitter released from neurons to relay information to another. It is stored in membranous sacs in the axon terminal called vesicles. There are thousands of GABA molecules in each vesicle. The vesicles fuse with the neuronal membrane for the release of GABA by neurons and then release it via exocytosis. It is released into the synaptic space and diffuses across synaptic space to the postsynaptic neuron. In human, GABA acts at the inhibitory synapse by binding to GABA receptors and this binding causes opening of ion channels to allow the flow of potassium ion out of the cell and chloride ion into the cell [11]. This action results in a negative change in transmembrane potential causing hyperpolarization and decrease the excitability of neurons (Fig. 2). The GABA that was released that did not bind to a receptor, is either degraded by enzymes in the synaptic cleft or taken back into presynaptic axon terminal by active transport through transporter or reuptake pump. In addition to the brain, GABA produced at a high level in the insulin-producing beta cells of the pancreas. Along with insulin, GABA is produced by beta cells and GABA binds to its receptors on the neighboring islet the alpha cells of the pancreas and inhibits them secreting glucagon. Replication and survival of beta cells can be stimulated by GABA and it also helps in the conversion of alpha to beta cells. It leads to a new treatment for diabetes.

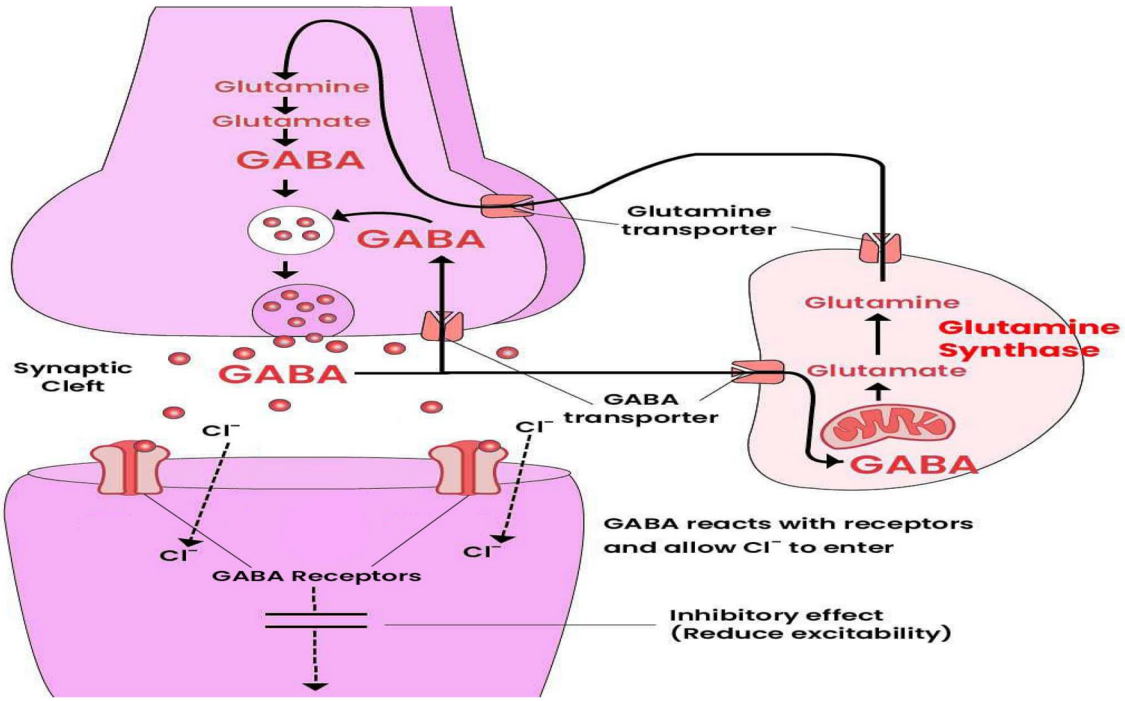

Fig. 2 Mechanism of action of GABA

GABA Pathway (GABA Shunt)

GABA is the main inhibitory neurotransmitter found predominantly in the brain. The major pathway of GABA consists of the conversion of alpha-ketoglutarate generated by the TCA cycle to succinate via glutamate, GABA and succinic semialdehyde. This pathway is known as GABA shunt (Fig. 3) a conserved pathway for prokaryotes and eukaryotes. During 1970, the study on guinea pig cells, the GABA shunt pathway was first described [12]. There are different types of enzymes involved in the GABA shunt. The first step is the production of glutamate from alpha-ketoglutarate by transamination reaction and the reaction catalyzed by glutamate dehydrogenase. The next step is the glutamate decarboxylation to GABA catalyzed by glutamate decarboxylase (GAD) and this step is irreversible. In this step glutamate decarboxylase consumes a proton and releases CO_2. The GAD enzyme is present in various organisms of all kingdom of life. In GABA synthesis GAD is a rate-limiting enzyme and it requires pyridoxal phosphate (PLP) as a cofactor [13]. Two isoforms of GAD, GAD67, and GAD65 are expressed by mammalian species. GAD67 gene and GAD65 gene located on chromosomes 2 and 10 respectively in humans. GAD67 synthesizes GABA in the brain, whereas GAD65 is the major GAD isoform in pancreatic cells. The third enzyme involved in the GABA shunt is GABA transaminase. In this step, GABA catabolism occurs and produces succinic semialdehyde (SSA) using enzyme GABA transaminase. The next step is the conversion of succinic semialdehyde to succinate by enzyme succinic semialdehyde dehydrogenase and it enters the TCA cycle. Succinate, an electron donor to the mitochondrial electron transport chain is the significant factor of the tricarboxylic acid cycle. In plants, animals [14, 15] and *Escherichia coli* [16] GHB dehydrogenase (GHBDH) convert SSA to γ-hydroxybutyric acid (GHBA). GAD is located in the cytosol and GABA transaminase and succinic semialdehyde dehydrogenase are located in mitochondria. The main role of GABA shunt is the production of GABA. Synthesis of GABA was also done through polyamine (putrescine and spermidine) degradation [17, 18] and under oxidative stress, it occurs by a non-enzymatic reaction from proline [19].

Microorganisms Producing GABA

GABA as an effective compound with bio-functions can be used as a drug with significant pharmacological effects. Besides, it is effective as a component of health food as well. In biological tissues, GABA is present in very low concentration so it is very difficult to be extracted sufficiently from natural organisms. In order to get GABA, an alternate method was necessary. Researchers turned to chemical and biological field and in the last two decades, they achieved good results. However the chemical synthesis has some drawbacks for the corrosive reactants, so the biological method got prominence in the GABA research. Microbial fermentation has a high transformation rate and convenient use, so it is regarded as an effective one to produce GABA in the biological method. Siragusa et al. [20] reported that *Lactobacillus delbrueckii* subsp. *bulgaricus* PR1, *Lactobacillus plantarum* C48, *Lactococcus lactis* PU1, *Lactobacillus brevis* PM17 and *Lactobacillus paracasei* PF6 isolated from various kinds of cheese produced GABA. Similarly the strain of *Lactococcus lactis* sub *lactis* was screened

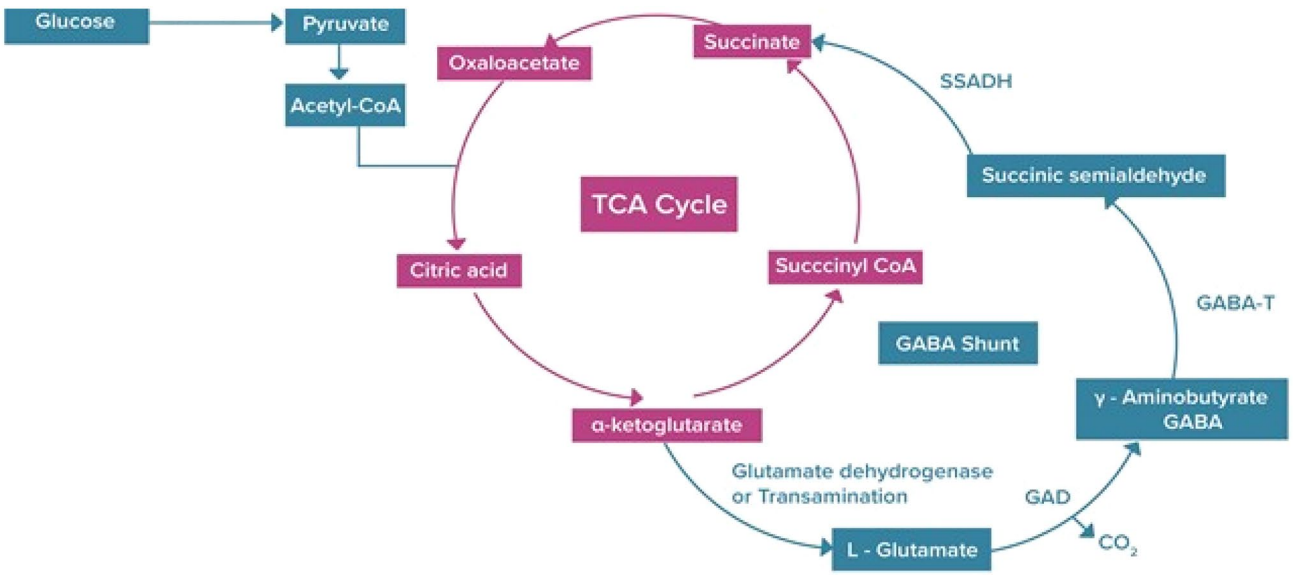

Fig. 3 Major metabolic pathway of GABA (GABA shunt pathway)

and selected with the best producers of GABA from cheese starters [21]. Other bacteria such as *Lb. brevis* [22–25], *Lb. plantarum* [26], *L.* sub *lactis* [27], *Lb. plantarum*, *Lb. brevis, Leuconostoc mesenteroides, Leuconostoc lactis, Weissella viridescens* [28], *Lb. buchneri* [29], *Lb. zymae* [30] were produced large amount of GABA from kimchi, traditional fermented food in Korea. Many food items can act as a medium for the production of GABA from *Lb. brevis* IF0-12005 in rice shou distillery rice (komusachusa) as an economic and simple process of GABA production [31].

As a perfect medium for GABA production by Lactic acid bacteria, fermented fish products are used. The bacteria *Lb. farcimini* D323 was one of the most efficient LAB strains in fermented fishery products with boiled rice [32] that can be used for GABA synthesized functional foods. Liao et al [33] investigated the effects of pre-processes such as immersing, germinating and cold shock before fermentation conditions of adzuki beans and cold treatment resulted in higher GABA accumulation using mixed cultures of *L. lactis* and *Lb. rhamnosus* compared to non-treated adzuki beans. GABA production by *Streptococcus salvarius* subsp *.thermophilus* via submerged fermentation was first reported by Yang et al [34] and their result indicated that *S. salivarius* subsp. *thermophilus* produced a large amount of GABA and had enormous potential to use as starter in the production of GABA-containing cheese, yogurt and other functional fermented foods. An efficient and simple fermentation process was developed for the production of γ-aminobutyric acid (GABA) by *Lactobacillus sakei* B2-16 and the successful result of GABA production up to plant scale strongly suggests that *Lb. sakei* B2-16 produces commercial GABA in the RBE-MSG medium and that can be used in industrial fields [35]. Some researchers reported that co-culturing of strains of lactic acid bacteria *Lb. delbrueckii* subsp. *bulgaricus* and *S. thermophilus* IFO13957 [36], *Lb. brevis* and *Lb. plantarum* from Egyptian dairy products [37] produced a large amount of GABA. These findings suggested that co-cultivation of both strains increase each other's acidification properties of the medium and production of acid resistance or GABA.

Apart from bacteria, GABA is also found in many fungi, yeast, and molds. The occurrence of Gamma-aminobutyric acid in a yeast *Rhodotorula glutinis* was reported as early as by Krishnaswamy and Giri [38]. Gamma-Aminobutyric acid (GABA) can be produced by *Monascus spp*, a type of fungi in solid and submerged cultures. GABA production reached 1396.04 mg/kg when the basic medium was supplemented with both $NaNO_3$ and $MnSO_4{\cdot}H_2O$ [39]. In the early phase of *Neurospora crassa* spore germination, the GABA pool was observed [40]. Kubicek et al. [41] investigated the GABA pool accumulation by the strain of *Aspergillus niger* during batch growth under manganese sufficient and deficient conditions. Masuda et al. [42] isolated *Saccharomyces*, *Candida utilis*, and *Candida fermanti* from the pacific ocean and produced a high concentration of gamma-aminobutyric acid. Dikshit and Tallapragada [43] reported that *Monascus sanguineus* was isolated from spoiled pomegranate and produced gamma-aminobutyric acid using coconut oil cake as a substrate. Production of GABA using *Monascus purpureus* by fermenting rice and nutrient media [44] as well as using *Rhizopus microsporus* strains by fermenting soybeans [45] has been demonstrated. Below Table 1 listed the GABA producing microorganisms and its source of isolation.

GAD Gene

This gene encodes glutamate decarboxylase (protein-coding gene) which is responsible for the production of gamma-aminobutyric acid from L-glutamic acid and is a major autogen in insulin-dependent diabetes. GAD is widely spread among eukaryotes and prokaryotes. In many microorganisms, this plays a vital role in biosynthesis and natural GABA accumulation. Numerous research reported that GABA producing ability of lactic acid bacteria and the presence of GAD activity in their cells. GAD is an intracellular enzyme that induces an acid stress response in lactic acid bacteria [47, 50]. GAD system is highly variable between species since some have one, two, or three decarboxylase followed by none, one, or two antiporters. In the case of *Mycobacterium tuberculosis*, it has a GAD gene that is not accompanied by an antiporter [75], However, *Listeria monocytogenes* normally has three decarboxylases and two antiporters [76]. Therefore, the chemical and physical properties of GAD of several species or strains differentiate considerably, which makes it possible to search for new GAD enzymes with a higher biotechnological value. Many investigators detected GAD gene sequence in different microorganisms which can indicate its ability to produce GABA at genetic level [20, 69]

Huang et al.'s [46] work indicated that *Lb. brevis* immobilization with higher glutamate decarboxylase activity (GAD) into ca-alginate gel beads offers high biotransformation of L-monosodium glutamate to GABA and offers a promising means of GABA production for industrial production. They have cloned full-length GAD from *Lb. brevis* using RACE PCR methods and the protein was successfully expressed in *E. coli* cells and result from their study suggested that recombinant GAD could be used for the industrial production of GABA. Brasca et al. [77] reported that *S. thermophilus* were preliminarily screened for the presence of the genes coding for glutamate decarboxylase (gadB*)* and showed the ability to produce γ-aminobutyric acid (GABA) production and Yunes et al. [78] investigated the presence of GAD gene and the GABA synthesizing ability of human-derived *Lb. plantarum*, *Lb. brevis*, *B. adolescentis*, *B. angulatum*, *B. dentium*, and other gut-derived bacterial species which may be an

Table 1 Gamma-amino butyric acid producing bacterium and its source of isolation

S. No	Microorganisms	Isolation source	References
1.	*Lactobacillus brevis*	Paocai	[46]
2.	*Lactobacillus brevis*	Kimchi	[22–25]
3.	*Lactobacillus brevis*	Quinoa sourdough	[47]
4.	*Lactobacillus paracasei, Streptococcus thermophilus, Leuconostoc mesenteroides, Lactobacillus rhamnosus, Lactobacillus plantarum, Pediococcus pentosaceus*	Cheese	[48]
5.	*Lactobacillus paracasei*	Traditional fermented fish	[49]
6.	*Lactobacillus brevis*	Fish intestine	[50]
7.	*Lactococcus lactis ssp lactis*	Cheese	[51]
8.	*Streptococococcus thermophilus*	Fish	[52]
9.	*Lactobacillus farciminis*	Fishery products	[32]
10.	*Lactobacillus brevis*	Human faecas	[53]
11.	*Lactobacillus plantarum*	Kimchi	[26]
12.	*Lactobacillus plantarum*	Honeybee	[54]
13.	*Lactococcus lactis sub lactis*	Cheese	[21]
14.	*Lactobacillus buchneri, Lactobacillus sp*	Cheese	[55]
15.	*Lactococcus sub lactis*	Kimchi	[56]
16.	*Lactobacillus paracasei, Lactobacillus delbrueckii* subsp.*bulgaris, Lactococcus lactis, Lactobacillus plantarum, Lactobacillus brevis*	Cheese	[20]
17.	*Lactobacillus plantarum*, *Lactobacillus brevis, Leuconostoc mesenteroides,Leuconostoc lactis,Weissella viridescens*	Kimchi	[28]
18.	*Lactobacillus buchneri*	Kimchi	[29]
19.	*Lactobacillus brevis, Lactobacillus plantarum*	Egyptian dairy products	[37]
20.	*Pseudomonas sp*	Sea water	[57]
21.	*Lactobacillus helveticus*	Koumiss	[58]
22.	*Lactobacillus plantarum*	Fermented beverage Marcha of Sikkim	[59]
23.	*Lactobacillus zymae*	Kimchi	[30]
24.	*Lactobacillus buchneri, Lactobacillus brevis,Weissella hellenica*	Traditional fermented food from japan	[60]
25.	*Lactobacillus brevis*	Fish	[61]
26.	*Lactobacillus sakei*	Jeot-gal, a korean fermented seafood	[62]
27.	*Lactobacillus futsaii*	Kung-Som	[63]
28.	*Saccharomyces cerevisae*	Fruit	[64]
29.	*Enterococcus avium*	Naturally fermented scallop solution	[65]
30.	*Lactobacillus curieae*	Stinky tofu brine	[66]
31.	*Enterococcus raffinosus*	Naturally pickled Chinese vegetables	[67]
32.	*Enterococcus avium*	Jeotgals, Korean traditional fermented and salted seafoods	[68]
33.	*Enterococcus faecium*	Traditional fermented food samples	[69]
34.	*Lactobacillus fermentum*	Chinese traditional fermented food pickled vegetable	[70]
35.	*Aspergillus oryzae*	Tane-koji	[71]
36.	*Saccharomyces,Candida utilis, Candida fermanti*	Pacific ocean	[43]
37.	*Lactic acid bacteria*	Kimchi, Jot-gal(traditional fermented foods)	[72]
38.	*Lactobacillus plantarum*	Dadih	[73]
39.	*Lactobacillus otakinesis, Lactobacillus paracaesai, Lactobacillus plantarum*	Azorean cheese	[74]

important feature for selecting probiotic bacteria. Tsuchiya et al [71] produced Gamma-aminobutyric acid from *Aspergillus oryzae* and they purified glutamate decarboxylase (GAD) from *A. oryzae* and characterized its biochemical and kinetic properties. Tavakoli et al. [79] identified the GAD gene from *Lb. casei* and a fragment containing this gene was successfully cloned in PGEM-T vector and this bacterium could possibly be used for industrial GABA production and also for the development of functional fermented foods. Taherzadeh et al. [80] cloned and sequenced the glutamate

decarboxylase gene from *Lb. delberckii* and *Lb. reuteri* and capacity of these bacteria open new perspectives on GABA-enriched functional foods. All results, therefore, suggested that strains with the highest GAD activity should be chosen to increase GABA content of fermented foods.

Factors Affecting GABA Production

The rate of GABA production by microorganism is affected by various fermentation factors, among which temperature, pH, time, and media additives of culture are common and essential. The conditions of fermentation can be optimized on the basis of the biochemical properties of GAD of microorganisms. Medium composition optimization for increasing GABA productivity and experiments to configure low-cost medium were carried out together for the industrial production of GABA [10, 81]. The composition of overall optimal media may vary depending on the strain of bacteria producing GABA.

pH has a very strongly marked effect on GABA production and it can regulate the biosynthesis of GABA in microorganisms. GABA production was considerably high (302 mM) at pH 5.0 when GABA producing the ability of *Lb. paracaesai* was compared with different pH (4–6) [49]. Production of GABA by *S. salivarius* sub species *thermophilus*Y2 has been increased by optimizing the fermentation conditions and by adding pyridoxal phosphate (PLP) and GABA output (7985 mg/liter) at pH 4.5 [34]. *Lb. delbrueckii* subsp. *bulgaricus* PR1, *Lb. parcaesai* PF6, *Lb. brevis* PM17, *Lb. plantarum* C48, *L. lactis* PU1 in cheese produced a large quantity of GABA (289–391 mg/kg) at a pH range of 4.68–5.70 [20]. The highest amount of GABA (7.2 g/l) produced by *L. lactis* was at 7.1, however, GABA production was reduced at pH above 8 [27]. In fermentation medium pH changes with time, initial pH impacts final GABA and timely adjustment of media pH should be made for optimal pH [10, 27].

An important factor in the GABA yield by fermentation is its incubation temperature. The high-efficiency glutamate conversion to GABA requires a high cell density and appropriate culture temperature and the maximum GABA (27.6 mg/ml) was produced at pH 3.5 and 30 ° C on 12th day of fermentation in the *Lb. brevis* GABA 100 fermenting black raspberry juice [10] and optimum temperature for GABA production using *Lb .buchneri* in MRS broth was at 30ºC and produced GABA at a concentration of 241 mM with 94% GABA conversion rate [29]. *Lb. brevis* immobilized whole cells at 40ºC produced 92% GABA after fermentation period of 8 h [46]. In *S. Salivarius* subsp *thermophilus,* the optimum temperature for GABA production was 37 °C [34] and the highest GABA, (303 mM) was produced by *Lb. paracaesai* NFRI 7415 at 37 °C, but GABA production and cell growth were significantly reduced at 43 °C [49]. Fermentation temperatures of 25 °C and 40 °C generally produce a high level of GABA within the temperature range.

In the fermentation and production of GABA, the time factor plays a significant role as temperature and pH. On the 15th day of fermentation, black raspberry juice fermented with *Lb. brevis* GABA 100 reached the highest GABA production at (25 °C pH 5.5) and (37 °C pH 5.5) and highest GABA was produced at 12th day when the sample was fermented at pH 3.5 and 30 °C [10]. In the fermentation of *L. lactis,* a considerable difference in the GABA yield was shown between different times of MSG added, since the highest GABA yield was obtained by adding MSG over 6 to 96 h during fermentation at 6-h interval of time [27]. The production of the highest GABA by microorganisms can also be based on suitable media additives and optimum additive time.

Microbial production of GABA by fermentation is affected by nutrient composition and culture additives. Other main factors that affect the GABA production during the fermentation are media additives such as glutamate and PLP as GAD coenzymes [34, 49] and the composition of media especially carbon, nitrogen, and other components can influence production quantity of GABA. *L. lactis* produced the highest amount of GABA (6.4 g/l) from the mixed ratio (33:58:9) of brown rice juice, germinated soybean juice and enzymolyzed skim milk, milk with enzyme deteriorated properties as a source of nitrogen and carbon [56].

The addition of glutamate enhanced the production of GABA in *Lb. paracaesai* and *Lb. brevis* [47, 49] after inoculation of the strain for 144 h in the medium containing 500 mM of glutamate, GABA concentration by *Lb. paracasei* NFRI 7415 reached 161 mM [49] *Lb. brevis* and *Lb. brevis* NCL912 also enhanced GABA production by the addition of glutamate [47]. However, GABA production by *S. salivarius* subsp. *thermophilus* Y2 was not significantly increased by the addition of 10–20 g of glutamate per liter of media, so these glutamate concentrations are not suitable for the production of GABA in this species [34]. Without the addition of glutamate, GABA could be produced from LAB using shochukasu as a growth medium. After 1 or 2 days of inoculation, GABA concentration reached 10.05 mM and 10.18 mM in komeshochukusu [31]. PLP is also used to increase GAD activity as a coenzyme [50]. During fermentation, GABA production increased and reached to 7333 mg/l by the addition of PLP in *Salivarius* subsp. *thermophilus* Y2 [34]. However, the GABA conversion rate was not increased by adding more than 0.6% glucose without ammonium sulfate [39]. The GABA production was enhanced by the addition of other substrates such 50% of tomokoji and wholemeal in *M. pilosus* IFO 4520 and *Lb. plantarum* C48 [6]. Therefore substrate concentration is important for achieving high GABA yield.

Functions of GABA in Microbial System

GABA is a four-carbon compound that is widely distributed in bacteria. In bacteria, it plays a metabolic role in the Krebs cycle. GABA has some functions in bacteria. It varies from strain to strain (Fig. 4). Numerous studies about GABA's role in human beings were already made but here we are trying to discuss GABA function in microbes. Acid tolerance is one of the main criteria for the identification of potential probiotic strains. One of the most important factors for bacteria to maintain neutral pH under acidic stress depends upon glutamate-antiporter reactions. In bacteria with the help of specific transporter, glutamate released into the cell and cytoplasmic decarboxylation occur which results in the consumption of intracellular proton. Through antiporter, reaction product GABA is exported from the cell and due to the removal of hydrogen ions, intracellular pH is increased. Extracellular pH is also increased due to the exchange of extracellular glutamate for more alkaline GABA (Fig. 5). Hence, the main function of glutamate decarboxylase is to control the pH of the bacterial environment by consuming hydrogen ions by the decarboxylation reaction. *E. coli*,

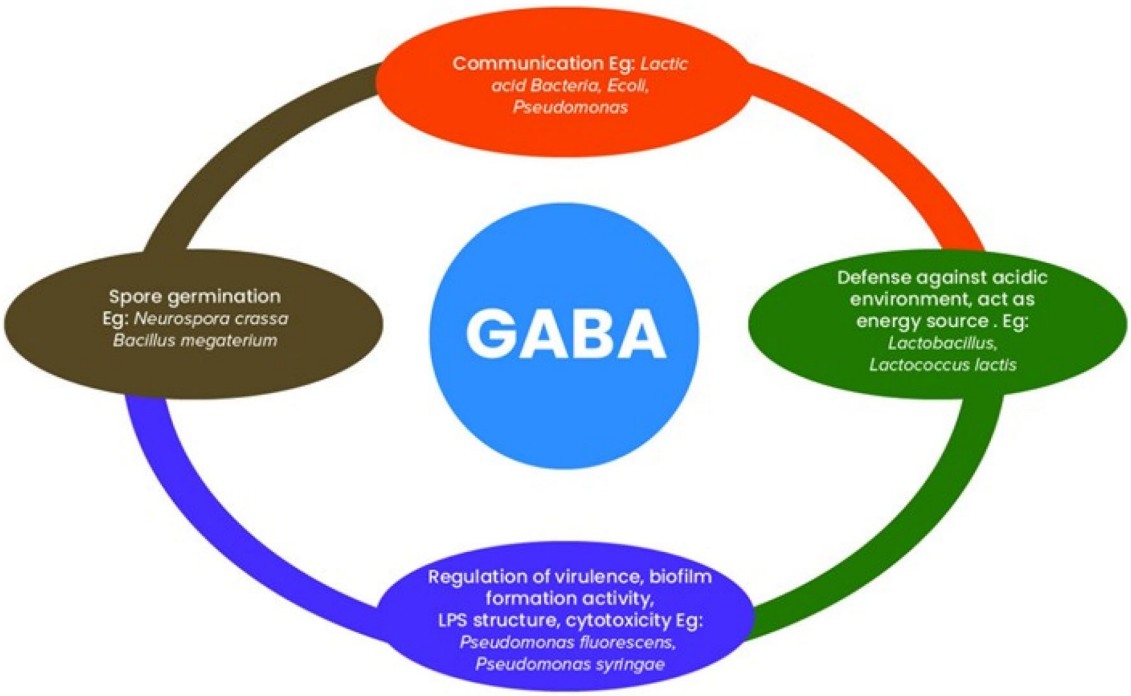

Fig. 4 Role of GABA in microbial systems

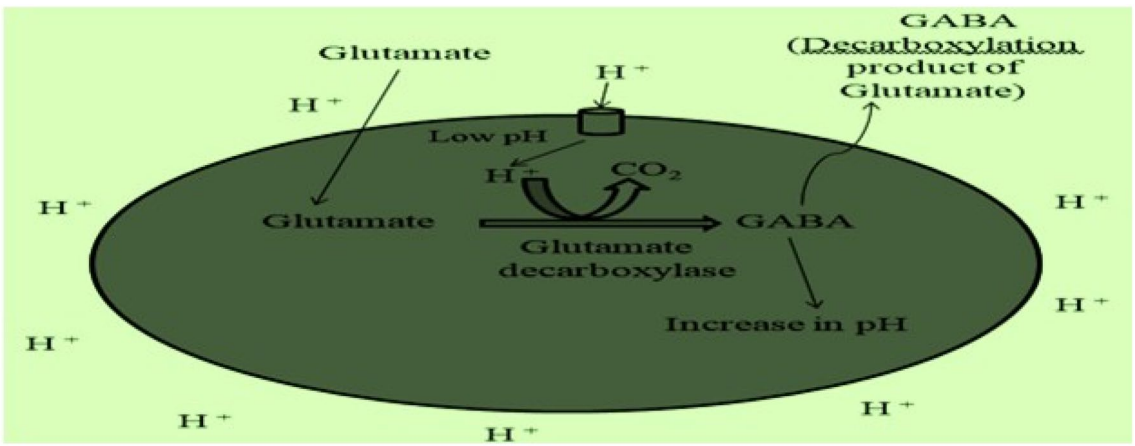

Fig. 5 Function of GABA in acid resistant mechanism

Shigella and lactic acid bacteria such as *Lactobacillus, L. lactis* [82–84] possess the gene for glutamate decarboxylase and expression of these genes require bacteria to survive under acidic pH. So increased GAD activity is critical to survive in acidic conditions and allows the bacterium to overcome the low pH environment of fermented foods, gastric juice, volatile fatty acids in the gastrointestinal tract if, for example, the producing strain was orally administered as a probiotic. GABA on virulence was investigated by Dagorn et al. [85] and they showed that GABA can reduce the virulence of different strains of *Pseudomonas fluorescens.* They also investigated the GABA effect on the mobility, growth kinetic, the binding potential on biotic and abiotic surfaces, surface polarity, biosurfactant production, biofilm formation activity, exoenzymes secretion in environmental and clinical strains of *P. fluorescens*. According to their result, LPS structure and cytotoxicity of *P. fluorescens* can be regulated by GABA. Chevrot et al. [86] revealed that plant GABA stimulated the inactivation of *N*-3-oxo-octanoyl-L-homoserine lactone (3-oxo-C8-HSL) and modulate quorum sensing in *A. tumefaciens.*

GABA functions as a molecule of communication between bacteria and their host and even between bacteria. Many bacteria including marine microorganisms [87], *Lactic acid bacteria* [20], *E. coli* [88], and *Pseudomonas* [89] which reported to synthesize GABA, a conserved and ubiquitous communication molecule like in eukaryotes. Foerster et al. [90] examined glutamate decarboxylase (GAD) in the spore germination of *Bacillus megaterium* and their findings suggest that spore germination in the strain of *B. megaterium* depends upon on the decarboxylation of endogenous L-glutamic acid and generation of gamma-aminobutyric acid. In *P. aeruginosa,* intracellular polyamine levels are controlled by GABA which act as an inducer for the enzymatic pathway [89] and it is also an intermediate metabolite of organic polycation catabolism.

Conclusion

The living cells of various organisms contain GABA which acts as a cerebral neurotransmitter in the central nervous system of animals. GABA makes an important position in human health due to its role as a tranquilizer, along with its curative quality in the treatment of epilepsy [91], inhibition of cancer cell proliferation, and its use is extensive in pharmaceuticals and functional foods. Growing demand increases commercial value for its mass production. Various methods are used to produce GABA, among which biosynthetic approach mainly microbial method is considered as more effective due to safety and eco-friendly. Hence, here we are focusing on GABA production and functions in different types of microorganisms. More studies are essential to find out other GABA functions in humans and microbes.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

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