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Gamma-Aminobutyric Acid (GABA): A versatile bioactive compound

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ABSTRACT

γ-Aminobutyric acid (GABA) is a potent bioactive compound, which has immense market demand due to its important physiological functions and positive health effects which aid in treatment or prevention of many diseases. The main physiological effects of GABA include neuronal modulation to improve nervous system disorders, regulation of anxiety, sleeplessness, mood disorders, protection against hypertension, diabetes, nephrotoxicity and cancer. It is most commonly produced via decarboxylation of glutamate by glutamic acid decarboxylase and this pathway is operational ubiquitously in plants, microbes and humans. However, lactic acid bacteria (LAB) have emerged as the efficient clade for GABA production and is most widely used for producing GABA-enriched products by fermentation. The present review addresses the importance of GABA as a therapeutic target as well as nutraceutical for providing various health benefits. The aspects related to its production by microbial fermentation have been elaborately discussed. Further, its newly emerged role as C4-platform chemical for production of bioplastics has been encompassed in its novel applications.

Keywords: Gamma-aminobutyric acid (GABA); C4-platform chemical; lactic acid bacteria; fermentation; functional foods; glutamic acid decarboxylase.

INTRODUCTION

γ-Aminobutyric acid (GABA), a non-proteinogenic amino acid serves several important physiological functions in microbes, plants and animals and thus, widely distributed in both prokaryotes and eukaryotes. Being, among the major inhibitory neurotransmitters, GABA is an integral component of central nervous system of mammals and present in ~40% of the synapses occurring in brain (Johnston, 2017). It plays a vital role in neuronal development, modulating synaptic transmissions and promoting the metabolism of brain cells (Kook and Cho, 2013; Ngo and Vo, 2019). Therefore, GABA has also been implicated in treatment of various neurological disorders viz. Parkinson's, Alzheimer's, Huntington's disease, dementia and bipolar disorders. Various plant derived products have been found to moderate the symptoms of neurodegenerative diseases and more specifically for Alzheimer's disease as discussed by Anand et al. (2017). The protective role of GABA in various neurodegenerative disorders has been reported by many studies viz. GABA enriched *Laminaria japonica* improved cognitive impairment and was helpful in protecting against

dementia (Reid et al., 2018). In another study, the neuronal cells were protected against neurotoxicant-induced cell death by culture extracts of *Lactobacillus buchneri* producing GABA (Cho et al., 2007). The anti-hypertensive activity of GABA is it's another important physiological function, which has made it a therapeutic target for pharmaceuticals. The high blood pressure is associated with various cardiovascular and kidney diseases and GABA enriched diets have proved to be an effective hypotensive agent. The milk fermented by *Lactococcus lactis* and *Lactobacillus plantarum* exhibited antihypertensive effect as it was enriched by GABA and exhibited Angiotensin-I Converting Enzyme (ACE)-inhibitory activity (Nejati et al., 2013).

GABA administration has also been found to useful in treating anxiety, depression, mood disorders and sleeplessness (Ngo and Vo, 2019). The administration of GABA enriched *Monascus*-fermented powder to rats as animal mode exhibited antidepressant effects as it helped in recovering the level of norepinephrine, 5-hydroxytryptamine and dopamine in hippocampus (Chuang et al., 2011). Similarly, in another study of black soybean milk fermented by *Lactobacillus brevis* FPA 3709**,** the GABA-enriched product showed antidepressant effect on swimming rat model (Ko et al., 2013). GABA has also been found to play an important role in ameliorating hyperglycaemia and exert anti-diabetic effects. The administration of GABA enriched yogurt by fermentation with *Streptococcus salivarius*, helped in enhancing the level of serum insulin and improving the complications of progressive type 1 diabetes (Chen et al., 2016).

Further, the pharmacological value of GABA is enhanced by its inhibitory effects on proliferation of metastatic cells. Recently, Li et al., (2019) reported that germinated brown rice fermented by *Lactobacillus acidophilus* and having enhanced GABA content, exhibited potential as dietary supplement for treating colorectal cancer. It was found to suppress preneoplastic lesions along with activating the apoptotic pathway. Similarly, in another study the administration of extraneous GABA helped in inhibiting colon cancer cell proliferation by disrupting MEK-EGR1 signalling pathway as well increased the sensitivity towards oxaliplatin, an anti-cancer drug (Song et al., 2016). The renoprotective effect of GABA, which is helpful in ameliorating nephrotoxicity or severe renal injury has also been validated by various studies (Ngo and Vo, 2019). The administration of GABA with estradiol exerted nephroprotective against renal ischemia-reperfusion injury (Talebi et al., 2016). Another study also reported that the administration of GABA to rat model of acute tubular necrosis helped in significantly ameliorating the cisplantin induced nephrotoxicity (Ali et al., 2015).

All the above studies exemplify the role of GABA as a bioactive compound which helps in prevention or aiding in treatment of several severe diseased conditions. Thus, a lot of commercial interest has aroused in production of GABA or formulation of GABA-enriched foods. The present review addresses the biosynthesis of GABA by microorganisms in comprehensive details. Further, the various applications of GABA especially as a bioactive compound or a functional food ingredient are encompassed. Apart from its applications in pharmaceuticals and nutraceuticals, its role as C4 platform chemical for the production of important industrial chemicals such as 2-pyrrolidone and biodegradable polymer such as nylon-4 has been elaborately discussed.

PRODUCTION OF GABA

The three main routes for production of GABA are: (i) chemical synthesis (ii) enzymatic biocatalysis and (iii) microbial fermentation. Various studies have reported different chemicals routes for synthetic production of GABA viz. a highly complex five step reaction involving nitrile reduction, ester hydrolysis and deethoxycarbonylation was used to synthesize GABA from a functionally modified intermediate obtained by alkylation of diethyl cyanomalonate with ethyl bromoacetate (Cook et al., 2010). In another approach, the carboamination reaction of alkenes, catalysed by copper complex transfers was used for

synthesis of GABA (Zhu et al., 2017). Lie et al., (2018) reported GABA production from glutamic acid, which was isolated from waste gluten. The isophorone was used as an inducer reagent and microwave-assisted decarboxylation reaction was used to produce GABA with short reaction time and yield of 63%. However, the production of various unwanted side-products, use of hazardous reagents and the complexity of multi-step chemical reactions favour the microbial biosynthetic routes over chemical synthesis (Xu et al., 2017). The enzymatic biocatalysis route involves GABA production from glutamic acid after decarboxylation, which requires catalysis by glutamic acid α-decarboxylase (GAD) along with pyridoxal-5'-phosphate (PLP), the co-enzyme. Nonetheless, the complexity and high purification costs of GAD along with its stability and reusability constraints favour microbial production by fermentation (Dhakal et al., 2012; Xu et al., 2017).

Among microbes, both bacteria and fungi are known to be good sources for GABA production. The fungi belonging to genera of *Monascus*, *Neurospora*, *Rhizopus* and *Aspergillus* are the main producers (Diana et al., 2014). However, among bacteria, lactic acid bacteria (LAB) genera are the most extensively investigated for GABA production. Since ancient times, fermentation of food products by using LAB as starter cultures have been very popular. The release of bacteriocins, exopolysaccharides, organic acids, aromatic compounds, polyols by LAB during fermentation help in improving aroma, texture, shelf life and health benefits of fermented products. Further, their GRAS (Generally Regarded As Safe) status and high tolerance to stress conditions adds to their potential as bio-factories for production of various high-value commodity chemicals viz. lactic acid, polyols, poly-*β*-hydroxybutyrate (PHB) (Hatti-Kaul et al., 2018; Sauer et al., 2017). Likewise, they are considered most potent for high titre GABA production. The strains such as *Lactobacillus fermentum, Lactobacillus lactis, Lactococcus lactis, Pediococcus pentosaceus, Lactobacillus reuteri, Bifidobacterium* sp., *Lactobacillus brevis, Pediococcus acidilactici* and *Lactobacillus sakei* are most popular LAB for GABA production (Diana et al., 2014; Li and Cao, 2010).

There are two main pathways i.e. glutamate decarboxylase (GAD) pathway and the putrescine (Puu) pathway, which are followed in the microbial production of GABA. The Puu pathway, involving two different paths, is a minor route which is found in *Aspergillus oryzae* and *Escherichia coli* but not in common producers such as *Bifidobacterium* or *Lactobacillus*. The first path involves transformation of Puu to γ-glutamyl-Puu, which further undergoes oxidation to yield γ-Glu-GABA, which is subsequently hydrolysed to yield GABA. In the second path, Puu is directly degraded to γ-aminobutyraldehyde, which is oxidised to yield GABA. The GAD pathway, used by majority of GABA producers, involves pumping of feedstock i.e. monosodium glutamate (MSG) or glutamate into the cell, followed by decarboxylation by GAD assisted by coenzyme i.e. pyridoxal-5-phosphate (PLP). Glu/GABA antiporter then exports the transformed product i.e. GABA into the extracellular matrix (Diez-Gutiérrez et al., 2019).

Most of the production studies on GABA production have been reported by submerged fermentation. Therefore, the fermentation conditions i.e. pH, temperature, cultivation time and composition of nutrient media critically affect the titre of GABA production and their optimisation becomes a prerequisite (Diez-Gutiérrez et al., 2019; Kook and Cho, 2013). The maintenance of optimal pH is very important as pH of fermentation media changes with time and affects the activity of GAD. Though the optimal pH for GAD activity varies with microbial species, generally alkaline pH especially above 8 is detrimental for GABA production as it activates GABA-decomposing enzymes viz. succinic semi-aldehyde dehydrogenase and GABA transaminase (Dhakal et al., 2012; Diez-Gutiérrez et al., 2019). A study reported that the challenge of requirement of acidic conditions, can also be overcome by site-specific mutation of two residues of GAD, which allowed *E. coli* GadB mutant to work optimally till pH 7 (Ho et al., 2013). Most of the studies of GABA production

have been optimally operational at temperatures ranging from 25°C to 40°C. Generally, LAB have complex nutritional requirements and thus, require MRS (Man, Rogosa and Sharpe) broth supplemented with glutamate or monosodium glutamate (MSG) and PLP for GABA production, which leads to high costs for fermentation process especially at industrial level (Yuan and Alper, 2019). Thus, efforts for cost effective production of GABA are being made which allows direct GABA production from glucose, derived from biomass sources rather than addition of MSG. In this context, a robust *Corynebacterium glutamicum* was engineered by expressing GAD from *E. coli*, which resulted in GABA production of 12.37 ± 0.88 g/l directly from 50 g/l glucose, without the requirement of addition of glutamate (Takahashi et al., 2012).

Solid-state fermentation (SSF) is another strategy which has proved to be effective in cost effective GABA production along with advantage of producing a spent residue rich in nutritional quality. The bio-based economical GABA production was achieved by SSF using toxic deoiled cottonseed cake as growth substrate by *Lactobacillus brevis.* Under optimized conditions, GABA production of 19.7 mg/g was obtained with simultaneous 70 % degradation of toxic gossypol, which was restricting utilization of this abundant agro-waste (Grewal and Khare, 2017). Similarly, 91% reduction in content of anti-nutritional glycosides i.e. convicine and vicine in faba bean (*Vicia faba* L.) was achieved by fermentation with *Lactobacillus plantarum* VTT E-133328 with concomitant production of 626±35 mg/kg GABA (Coda et al., 2015). The SSF of coconut oil cake by *Monascus sanguineus* resulted in GABA production of 15.53 mg/gds (Dikshit and Tallapragada, 2015). A functional food for preventing hypertension was formulated by SSF of lentil (*Lens culinaris* L.) with *Bacillus subtilis* which exhibited 39% angiotensin I-converting enzyme inhibitory (ACEI) activity along with GABA production of 6.54 mg/g (Torino et al., 2013).

APPLICATIONS OF GABA

GABA enriched functional foods

Though GABA is naturally present in some fruits and vegetables, it exhibits little biological activity as its concentration is quite low ranging from 0.03 to 2.00 μmol/g (Kook and Cho, 2013). Therefore, the formulation of GABA enriched foods by fermentation is gaining high popularity due to the numerous health benefits they offer due to physiological functional roles of GABA. Many GABA enriched food products have been prepared by fermentation with GRAS organisms and available commercially. These functional foods exhibit a wide spectrum ranging from cereal-based products (wheat sourdough, bread, quinoa flakes, brown rice, fermented oats etc.), dairy products viz. cheese, milk, yogurt, legume based such as *adzuki* beans, black soybean and tempeh-like fermented soybean etc. (Quílez and Diana, 2017). The use of these foods in aiding treatment or prevention of various diseased states has further increased their nutraceutical value.

GABA as C4 platform chemical for production of high-value commodity chemicals

A new interest in demand of GABA has been aroused by its role as C4 platform chemical, wherein it serves as feedstock for synthesis of 2-pyrrolidone, polyvinylpyrrolidone and nylon 4, a biodegradable polymer for production of bioplastics (Diez-Gutiérrez et al., 2019; Wendisch et al., 2018). Conventionally, polyamides like nylon-4 are synthesized from petro-resources involving toxic precursors or intermediates. However, the bio-based routes offer a sustainable and eco-friendly alternative and thus, it has evoked great research interest in production of bio-based platform chemicals. In this context, cottonseed cake was used for growth of *Lactobacillus brevis* and microbially produced GABA was used for synthesis of 2-pyrrolidone, which serves as precursor for synthesis of nylon 4 (Grewal and Khare, 2017). In another study using genetic engineering, a recombinant *E. coli* expressing GAD from *Lactococcus lactis* was used for microbial production of GABA. The produced GABA was

used to synthesize 2-pyrrolidone, which was further polymerized to obtain nylon 4 (Park et al., 2013).

CONCLUSIONS

The use of bioactive compounds as therapeutics for managing various diseases and as nutraceuticals for providing health benefits is gaining immense popularity. In this context, GABA has emerged as versatile bioactive compound to develop enriched food products with various beneficial health effects and thus, has high demand in food industry. The LAB due to their GRAS status are most popularly used as starter cultures for fermentative production of GABA. The fermentation conditions i.e. pH, temperature, incubation period, feedstock used and the optimal activity of glutamate decarboxylase along with concentration of pyridoxal 5'-phosphate play a critical role in obtaining high titres of GABA production. The use of metabolic engineering to improve the yield and achieve cost effective production is being actively pursued. Apart from its nutraceutical role, there has been a further impetus on its production due to its use as feedstock for synthesis of high-value commodity chemicals viz. 2-pyrrolidone, polyvinylpyrrolidone and nylon 4. Their production by microbially produced GABA provides a sustainable and eco-friendly alternate to synthetic route derived from depleting petro-reserves.

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