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L-Theanine: An astounding sui generis integrant in tea

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ABSTRACT

L-theanine (L-Th), a non-protein amino acid present in tea, is a valuable nutraceutical product with unique health benefits and used as an additive in food industry. L-Th enhances the umami taste but its use is limited due to its inadequate production. Different extraction approaches from tea shoots, chemical synthesis to microbial transformation have been tried to meet its demand. *In vitro*, *in vivo* as well as clinical studies have shown its positive effect in regulating CNS disorders. L-Th has become choice ingredient in CNS active products due to its anti-stress and neuroprotective role in dementias particularly in retrogression of Alzheimer's. L-Th biochemically modulates various anti-neoplastic agents by increasing their bioavailability in tumour cells. The review, is an effort to condense the recent research on L-Th highlighting its biological resource, plausible role in tea plant, production approaches, its physiological role on human health and future prospects.

1. Introduction

Changes in lifestyle, dietary habits and increased life expectancy has led to increased prevalence of lifestyle diseases such as obesity, diabetes, hypertension and hyper-cholestemia. The growth of global nutraceuticals market in last two decades has documented an increase in the Annual Average Growth Rate from 7.3% in 1990–2002 to 14.7% in 2002–2010 (Frost, 2011) and is expected to reach US $250 billion by 2018 (Stirling & Kruh, 2015). More than 500 research articles on L-Th and nearly 300 review articles on tea have reported beneficial effects of L-Th on CNS and emphasized on its commercial production (Lardner, 2014; Williams et al., 2016). Substantial information on L-Th is available from different sources in public domain, but comprehensive information does not exist at one place. This review, therefore, focuses to provide comprehensive information on the source of L-Th, its role in the tea plant, production and detection approaches, biochemistry and pharmacological properties along with future research perspectives.

2. Occurrence, absorption and metabolism of l-theanine

L-Th, not only enhances the flavour and quality of infused tea, but also has important physiological role in tea plant. L-Th is chemically 2-amino-4-(ethylcarbamoyl)-butyric acid, a chiral compound that exists in L-(S) enantiomeric form in nature. L-Th is synthesized from glutamic acid and ethylamine by enzyme theanine synthetase in roots of the tea plants, which is then translocated to apical bud and subtending three leaves (Fig. 1). L-Th accumulates in the developing shoots which are also the principal site for polyphenol synthesis (Walter, Puangrat, & Philip, 1986). On exposure to sunlight, L-Th gets hydrolysed to its precursors and liberates glutamine and ethylamine which serve as precursor for catechin synthesis. In tea plant, the role of L-Th is to detoxify ammonia absorbed by roots and convert it to other nitrogenous compounds. L-Th serves as a reservoir for nitrogen and an initiator for skeletal carbon compounds during germination (Deng, Ogita, & Ashihara, 2010). Accumulation followed by catabolism of L-Th and other nitrogenous compounds during slow division of meristematic tissues in young tea plant indicate its role in developmental physiology

Abbreviations: AIDA, alanine decarboxylase; ALT, alanine transaminase; 5′-AMP, adenosine monophosphate; L-Th, L-theanine; ADHD, attention deficit hyperactivity disorder; ADA, adriamycin; AD, Alzheimer disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ATP, adenosine triphosphate; cAMP, cyclic-adenosine monophosphate level; CNS, central nervous system; CRF, corticotrophin releasing factor; DNA, deoxyribonucleic acid; DOX, doxorubicin; EGCG, epigallocatechin gallate; GOGAT, glutamine oxoglutarate aminotransferase; GDH, glutamate dehydrogenase; GGT, γ-glutamyl transpeptidase; GS, glutamine synthetase; GMAS, γ-glutamylmethylamide synthetase; GABA, γ-aminobutyric acid; 5′-IMP, inosine monophosphate; 5-HIAA, 5-hydroxyindole acetic acid; 5-HT, serotonin; HPLC, high performance liquid chromatography; HPTLC, high performance thin layer chromatography; MAE, microwave-assisted extraction; NE, norepinephrin; NMDA, *N*-Methyl-D-aspartic acid or *N*-Methyl-D-aspartate; OPA, o-phthalialdehyde; OFC, orbito-frontal cortex; PDA, photodiode array detectors; PITC, phenylisothiocyanate; P-gp, P-glycoproteins; SWE, sub-critical water extraction; SUMO, small-ubiquitin related modifier; SFE, supercritical fluid extraction; SHR, spontaneously hypertensive rats; TS, theanine synthetase; ThYD, theanine hydrolase; TLC, thin layer chromatography; UAE, ultrasound-assisted extraction; UHPE, ultrahigh pressure extraction; WKR, Wistar Kyoto rats

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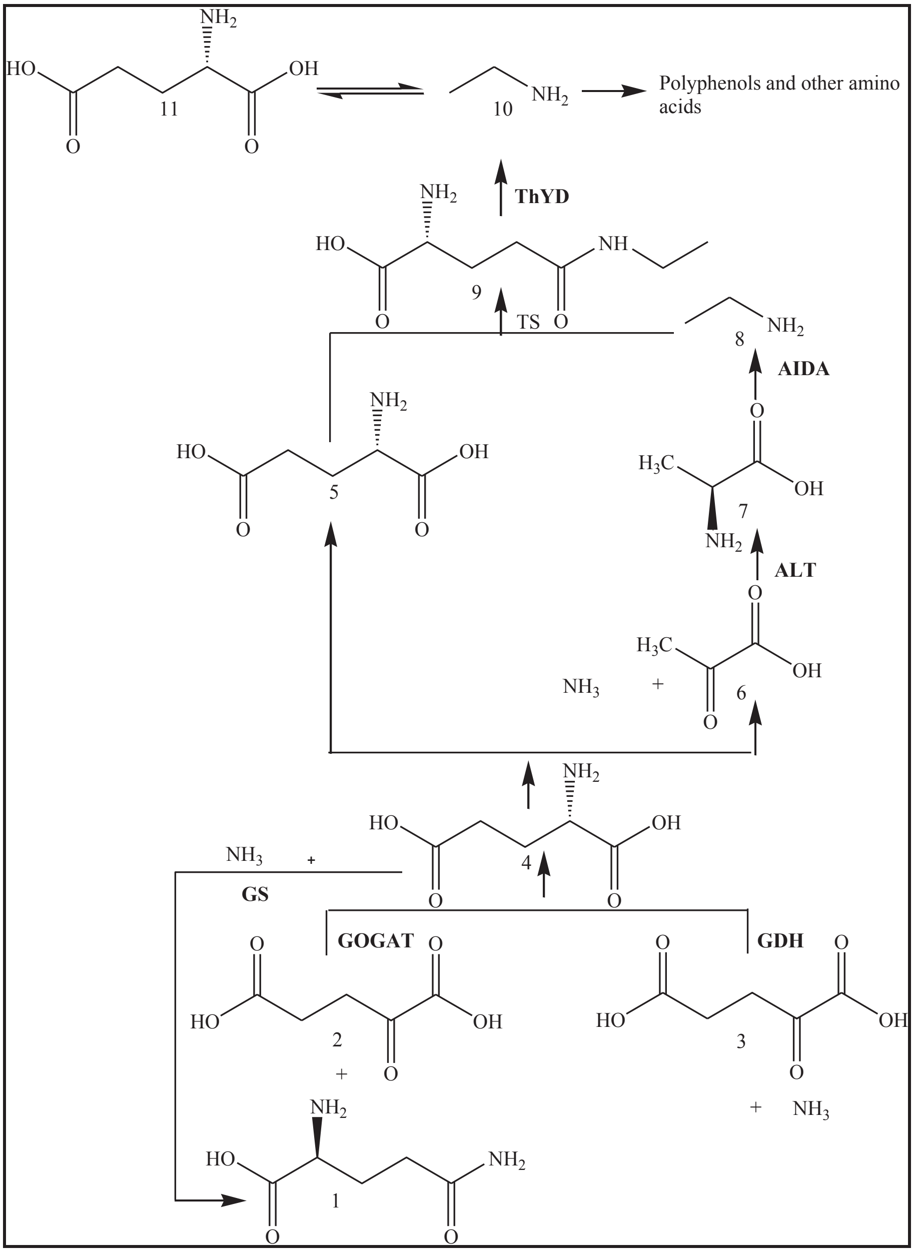

Fig. 1. Bio-synthetic pathway of L-theanine in *Camellia sinensis*. 1. Glutamine, 2,3. Oxoglutarate, 4,5. Glutamate, 6. Pyruvate, 7. L-alanine, 8. Ethylamine, 9. Theanine, 10. Ethylamine, 11. Glutamate. GS: Gluamine synthetase; GOGAT: Glutamine oxoglutarate aminotransferase; GDH: Glutamate dehydrogenase; ALT: Alanine transaminase; AIDA: Alanine decarboxylase; TS: Theanine synthetase; ThYD: Theanine hydrolase. The figure is based on the information provided in Shi et al., 2011 with permission.

of the plant (Walter et al., 1986). The content of L-Th varies with the type of tea cultivar, manufacture process i.e., green and black teas and infusion preparation method. A standard 200 mL cup of tea (500 mg of green and black tea) brewed at 80 °C for 2 min contains 7.9 and 24.2 mg of L-Th in green and black tea, respectively. Type of manufacture and packaging influences L-Th content in a cup in the order: tea bags (24.6 mg) > black tea (24.4 mg) > white tea (11.5 mg) > speciality black tea (10.9 mg) > green tea (7.9 mg). Addition of semi-skimmed milk during tea infusion preparation significantly lowers L-Th content in a tea cup compared to cup infused with skimmed or full fat milk. Addition of sugar during tea infusion preparation, however, did not significantly affect L-Th content. Higher content of L-Th was found in the cup prepared with vigorous agitation (Keenan, Mike, Jones, Rogers, & Priestley, 2011). Once tea is consumed, L-Th gets rapidly absorbed through microvilli via intestinal epithelial cells from where, it is transported to the brain tissues as it crosses the blood brain barrier. In brain tissues, L-Th concentration reaches to maximum in 5 h and effects metabolism and secretion of various neurotransmitters within 30 min. L-Th catabolises to ethylamine and glutamic acid by amide hydrolysis in kidneys through phosphate independent glutaminase pathway excreting ethylamine into urine and glutamic acid was converted into glutamyl peptides via γ-glutamyl transferase reaction *in vivo* (Tsuge, Sano, Hayakawa, Kakuda, & Unno, 2003).

3. Biochemistry behind the "umami" taste

"Umami" means delicious, savoury, broth-like or meaty flavour and has been accepted as the fifth taste in addition to sweet, salt, sour and bitter. L-Th along with 5′-IMP produced from 5′-AMP during tea processing impart umami flavour to teas. In oral cavity, various G-protein-coupled receptors (GPCRs) like truncated type 1 and 4 metabotropic glutamate receptors contain heterodimer T1R1 and T1R3 subreceptors which respond specifically to umami stimuli (Pin, Galvez, & Prezeau, 2003). Interaction of heterodimer taste receptors T1R1 and T1R3 with G receptors modulates cAMP and stimulates phosphokinase C which causes channel modulation in CNS and membrane depolarization. The decrease in cAMP results in closure of cyclic nucleotide-gated channels releasing neurotransmitters like serotonin and norepinephrin via gap