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**GENETIC MECHANISMS OF THE BIOSYNTHESIS
OF CATECHINS, CAFFEINE AND L-THEANINE IN THE TEA
PLANT *Camellia sinensis* (L.) Kuntze**
(review)

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Abstract

Catechins, caffeine and L-theanine are the main secondary metabolites of the tea plant *Camellia sinensis* (L.) Kuntze. They play a key role in shaping the taste, nutritional and medicinal value of tea (W.J.M. Lorenzo et al., 2016; Z. Yan et al., 2020). In addition, they are involved in the regulation of plant life, in particular, in the processes of adaptation to extreme environmental conditions (Y.S. Wang et al., 2012; L.G. Xiong et al., 2013; G.J. Hong et al., 2014). The above determines the interest in the physiological, biochemical and molecular mechanisms of the production of catechins, caffeine and L-theanine, to increase their accumulation in the plant (R. Fang et al., 2017; W. Kong et al., 2022), as well as to studying their participation in plant response to stress (P.O. Owuor et al., 2010). In the recent 5 years, a lot of new knowledge has been gained on the genes for the biosynthesis of catechins, L-theanine and caffeine, but there are no new reviews that generalize these new data and connect them with new data on the regulation of stress responses in tea. The purpose of this review is to analyze and summarize current data on the genetic mechanisms of the biosynthesis of catechins, L-theanine and caffeine in tea plant tissues, as well as their relationship with genes that regulate abiotic stress responses. The biosynthesis of catechins is carried out along the phenylpropanoid and flavonoid pathways (A. Laura et al., 2019; S. Alseekh et al., 2020) with the participation of the chalcone synthase (*CHS*), anthocyanidin synthetase (*ANS*), anthocyanidin reductase (*ANR*), and leucoanthocyanidin reductase genes (*LAR*) (J. Bogs et al., 2005). The accumulation of catechins in the tea plant involves transcription regulation factors of the MYB family, which regulate the expression of the *PAL*, *F3'H*, and *FLS* genes (C.-F. Li et al., 2015). Caffeine formation occurs mainly in tea leaves during purine modification (H. Ashihara, 2015) involving the *IMPDH* (Inosine monophosphate dehydrogenase), *SAMS* (Synthetase gene family), *MXMT* (7-methylxanthine methyltransferase), and *TCS* (tea caffeine synthase) genes. There are already 132 known transcription factors belonging to 30 families (including those encoded by genes of the *bZIP*, *bHLH* and *MYB* families), which are associated with the expression of caffeine biosynthesis genes (C.-F. Li et al., 2015). In *C. sinensis*, the biosynthesis of L-theanine from glutamate with the participation of pyruvate is controlled by a cascade of genes, the main of which are *GS* (glutamine synthetase), *GOGAT* (glutamate synthase), *GDH* (glutamate dehydrogenase), *ALT* (alanine transaminase), *ADC* (arginine decarboxylase), and *TS* (theanine synthetase) (C.Y. Shi et al., 2011; Y. Li et al., 2019). The regulation of these genes is conducted by more than 90 transcription factors — members of the *AP2-EREBP*, *bHLH*, *C2H2* and *WRKY*, *bZIP*, *C3H*, and *REM* families (C.-F. Li et al., 2015). The influence of stress conditions (drought, cold, salinity, nutrient deficiency) on accumulation of these biologically active substances is discussed. Nevertheless, the relationships between the expression of the metabolism genes of the studied compounds and transcription factors remain insufficiently studied; as well as changes in regulatory networks for the biosynthesis of valuable metabolites of tea plants under various environmental stresses.

Keywords: *Camellia sinensis* (L.) Kuntze, secondary metabolites, alkaloids, amino acids, catechins, L-theanine, caffeine, metabolite genes, gene expression, transcription factors, drought, low temperatures, salinity, nutrients

A drink from the young shoots of tea plants (*Camellia sinensis* L.) is widespread throughout the world and is highly valued due to a wide range of beneficial properties of a complex of substances (phenolic compounds, alkaloids, essential oils, essential amino acids, carbohydrates, mineral salts, vitamins, pectins, pigments, enzymes) [1]. Many of these components (approx. 700) are biologically active [1]. The substances contained in tea affect the heart activity and the function of the human nervous system [2], increase the efficiency of muscle tissues [3], induce vigor and stimulate mental activity [4, 5], strengthen the walls of blood vessels and capillaries [6], exhibit anti-radiation, bacteriostatic and bactericidal properties [7-10], activate the immune system and contribute to the prevention of certain types of cancer [9].

Catechins, which are phenolic compounds, and the alkaloid caffeine (these substances are secondary metabolites), as well as the unique amino acid L-theanine (found only in tea plants and not synthesized in the human body) play a key role in the formation of taste, food and nutrition. medicinal value of tea [2, 8, 10]. These plant metabolites are used in the manufacture of pharmaceuticals, food supplements, flavorings and other products [11, 12]. The content of these substances in the tissues of tea plants (and, accordingly, in the resulting products) is determined by the genotype [13, 14], growing area [15-18], harvesting season [19-22], elemental composition of leaves [23-26], the age of the tea leaf [27], the terms and methods of its processing and storage [28-30]. In addition, the accumulation of biologically active substances is significantly affected by the amount and composition of nutrients entering the soil with fertilizers [31-35], which creates opportunities for managing this process.

Secondary metabolites exhibit adaptogen properties, mitigating the effects of stress that plants experience when exposed to high and low temperatures [36-39], ultraviolet radiation [40, 41], in vitro osmotic shock [42-44], pathogen infection [45, 46], mineral deficiencies [47, 32], lighting levels and genetic factors, other factors [48-51].

The main pathways for the biosynthesis of catechins, L-theanine, and caffeine from the tea plant have been detailed in recent decades, but the mechanisms of regulation of ongoing biochemical processes have not yet been sufficiently studied [41, 52-55]. Thus, the gene networks responsible for this in *C. sinensis* have been identified relatively recently [56, 57]. Transcriptome studies have identified metabolic pathways and key genes involved in the biosynthesis, transport, and metabolism of catechins, caffeine, and L-theanine [58-61], which are discussed in more detail below.

Over the past 5 years, a lot of new knowledge has been obtained about the genes for the biosynthesis of catechins, L-theanine, and caffeine, but there are no new reviews in the world literature that summarize this information and link it with new data on the regulation of stress responses in tea.

The purpose of this review is to analyze and summarize current data on the genetic mechanisms of the biosynthesis of catechins, L-theanine, and caffeine in tea plant tissues, as well as their relationship with genes that regulate abiotic stress responses.

Biosynthesis of major secondary metabolites in tea plants.
Catechins. These phenolic compounds belong to one of the most common classes of plant secondary metabolites. Catechins make up 12-24% of the dry weight of a tea leaf [58] and determine the strength and astringency of the resulting drink by 70-75% [62, 63]. Tea plant catechins are represented by four simple forms, the

(+)-catechin (C), (-)-epicatechin (EC), (+)-gallocatechin (GC), (-)-epigallocatechin (EGC), and their galloyl derivatives (-)-catechin-3-gallate (CG), (-)-epicatechin-3-gallate (ECG), (-)-gallocatechin-3-gallate (GCG), (-)-epicalocatechin-3-gallate (EGCG). The properties of catechins are mainly determined by the number and position of the hydroxyl group, which provides binding and neutralization of free radicals [64, 65]. In vitro, tea catechins have been shown to serve as electron donors and effective quenchers of reactive oxygen species, including superoxide anion, peroxy radicals, and singlet oxygen [66].

The biosynthesis of catechins, which is currently well understood, occurs via the phenylpropanoid and flavonoid pathways [41, 67, 68]. The flavonoid biosynthetic pathway begins with the formation of chalcone with the participation of chalcone synthase encoded by the *CHS* gene, the expression of which correlated with the content of flavonoids in plants [69-71]. In several plant species, more than one copy of *CHS* has been identified in the genome [72, 73]. In *C. sinensis*, three copies of the *CHS* gene (*CHS1*, *CHS2*, and *CHS3*) were found, the expression of which also correlated with the accumulation of catechins in leaves and shoots [74], and the expression profiles, according to G.E. Mamati et al. [75], depended on leaf age. However, it is still unknown which of the three *CHS* genes plays a key role in catechin biosynthesis in *C. sinensis*.

In addition to *CHS*, the genes of flavonoid 3'-monooxygenase (*F3'H*), flavanol synthase (*FLS*), anthocyanidine synthetase (*ANS*), anthocyanidin reductase (*ANR*), and leucoanthocyanidin reductase (*LAR*), phenylalanine ammonium lyase (*PAL*) genes are involved in the biosynthesis of catechins. The *PAL* gene product catalyzes the first step of metabolism in the phenylpropanoid pathway. *F3'H* and *FLS* encode enzymes for the synthesis of flavanols in the flavonoid pathway. *ANS* catalyzes the conversion of leukocyanidins to anthocyanidins [76]. The *ANR* gene is involved in the biosynthesis of flavan-3-ol monomers, namely, in the conversion of anthocyanidin to epicatechin [77]. The *LAR* gene product catalyzes the conversion of leukocyanidin, leukodelphin, or leukopelargonidin to the corresponding 2,3-trans-flavan-3-ols [78]. All these genes play an important role in determining the composition of catechins in tea leaves [41, 79-81]. L. Zhang et al. [82] found a positive correlation between the expression intensity of the *CHS1*, *CHS3*, *ANR1*, *ANR2*, *LAR* genes and the total content of catechins. The expression level of the *ANS* gene had a positive relationship with the accumulation of simple catechins, while the *ANR1*, *ANR2*, and *LAR* genes had a positive relationship with the content of (-)-epigallocatechin-gallate and (-)-epicatechin-gallate [82]. It has been suggested that the most important genes for catechin biosynthesis in tea plants are the *F3'H* and *ANS* genes, the expression of which significantly increased in the autumn period simultaneously with the accumulation of catechins [83]. However, there is still very little data on the relationship between the expression of these genes and the composition and quantitative ratio of catechins in the tea plant. It is assumed that the expression of genes involved in the biosynthesis of phenolic compounds is regulated by transcription factors *MYB*, *bHLH*, *WRKY*, and other transcription factors associated with ABA-mediated plant response to stresses [84-87]. Thus, the *MYB* family genes are involved in the regulation of the expression of flavonoid biosynthesis genes (*PAL*, *F3'H*, and *FLS*) in the tea plant, which confirms the importance of *MYB* transcription factors in the control of flavonoid accumulation. In particular, in tea plants, the genes *CsMYB8*, *CsMYB99*, *MYB23* (*MYB* family), *bHLH96* (*bHLH* family), and *NAC008* (*NAC* family) are involved in the regulation of flavonoid biosynthesis, including catechins, anthocyanins, and flavanols [88, 89]. Increased expression of these transcription factors has been

positively correlated with catechin accumulation [88, 89]. A total of 206 transcription factors from 33 families have been reported to be associated with changes in the functional activity of 36 flavonoid biosynthetic genes [57]. It is recognized that at present the mechanisms of regulation of the biosynthesis and transport of flavonoids and anthocyanins are still insufficiently studied [89].

Caffeine (1,3,7-trimethylxanthine). This bioactive compound, synthesized by *C. sinensis*, is a purine alkaloid widely used as a stimulant and drug ingredient [90]. Both in terms of accumulation in the plant and in terms of pharmacological action, it is the dominant among all tea alkaloids [1]. Caffeine adds astringency to the tea infusion and also significantly affects its strength [29]. In addition, the caffeine content characterizes the activity of physiological processes in plants, in particular, redox and enzymatic reactions, and protein metabolism [90]. The caffeine content averages 3% of the dry weight of the tea leaf and, depending on a number of factors (environmental conditions, genetic and geographical factors), ranges from 1.5 to 4.5% [30, 90].

Caffeine is predominantly synthesized in young plant leaves from purine nucleotides in the reactions of adenine metabolism [91]. The main pathway of caffeine biosynthesis includes a series of sequential transformations xanthosine (XR) → 7-methylxanthosine (7-mXR) → 7-methylxanthine (7-mX) → theobromine (Tb) → caffeine (Cf) with the participation of the N-methyltransferase enzyme encoded by the *NMT* gene, which is also called the *TCS* (caffeine synthetase) gene [92-94]. N-methyltransferase exhibits transmethylation activity in two steps, catalyzing the conversion of 7-mX to Tb and Tb to Cf [95]. The genes *IMPDH* (inosine-5-monophosphate dehydrogenase), *SAMS* (S-adenosyl-L-methionine synthase), *MXMT* (7-methylxanthine methyltransferase) are also involved in the biosynthesis of caffeine. The study of the activity of allelic variants of the *TCS1* gene in tea plant populations confirmed that the caffeine synthetase enzyme determines the caffeine content in plant tissues. According to P. Li et al. [88], the *MYB* family includes the main transcription activators of the *TCS1* gene, while *CsMYB184*, *CsMYB85*, and *CsMYB86* play a key role in the regulation of caffeine biosynthesis [96]. Transcription factors of the *AP2/ERF*, *WRKY*, *bHLH*, *MYB*, *bZIP*, *TFIIIA*, and AT-hook families regulate the expression of structural genes of related synthetases involved in alkaloid biosynthesis [97]. For example, gene products of the *GATA* and *bHLH* families bind to the transcription initiation sites of 12 major caffeine biosynthesis genes of the AMPD family (encoding adenosine 5'-monophosphate deaminase enzymes), affecting their expression [98]. Recognition sites have recently been identified for the *MYB184* gene product, which exhibited high promoter activity, increasing *TCS1* gene expression by 4.7 times [96]. Transcriptomic studies of tea plant tissues at different stages of development have revealed regulatory networks that include 132 transcription factors from 30 families associated with the expression of 24 genes for caffeine biosynthesis [57]. Most of these transcription factors belong to the *bZIP*, *bHLH* and *MYB* families.

An analysis of tea varieties with different caffeine content showed that transcription factors of the *NAC* family are associated with the biosynthesis of purine alkaloids (99). One of the genes of this family is *CsNAC7*, according to W. Ma et al. [100], positively regulates the activity of the gene of the main enzyme of caffeine biosynthesis, tobacco N-methyltransferase *yhNMT1*. An analysis of the functional activity of *CsNAC7* showed that its transient overexpression could significantly enhance the expression of *yhNMT1* in tobacco leaves [96]. However, the relationship between the functional activity of caffeine metabolism genes and transcription factors requires further study. In particular, there is insufficient data

on changes in the regulatory networks for the biosynthesis of this alkaloid under nitrogen deficiency, which affects the productivity of tea plants.

L-Theanine (5-N-Ethylglutamine). This amino acid accounts for up to 50% of the total amino acids in black tea and 1-2% of the dry weight of green tea [101-103]. It gives a sweet and savory flavor to the tea drink [9, 104]. L-theanine is formed in roots, from where it is transported through the phloem to growing shoots and accumulated in young leaves [90, 105]. In *C. sinensis*, the formation of L-theanine from glutamate with the participation of pyruvate is controlled by a cascade of genes, the main ones being *GS* (glutamine synthetase), *GOGAT* (glutamate synthetase), *GDH* (glutamate dehydrogenase), *ALT* (alanine transaminase), *ADC* (arginine decarboxylase), and *TS* (theanine synthetase) (56). L-theanine can be hydrolyzed to ethylamine and then reused as a precursor in catechin biosynthesis, which has been noted with prolonged exposure to sunlight [54]. The conversion of glutamine and ethylamine to L-theanine in *C. sinensis* is carried out by the enzyme theanine synthetase (TS), which has a very high degree of homology with glutamate synthetase (GS) [54]. Glutamine, a precursor of L-theanine, is synthesized with the participation of glutamine-2-oxoglutarate aminotransferase and glutamate dehydrogenase [105]. Another precursor of L-theanine, ethylamine, is formed by the decarboxylation of alanine (Ala), which is catalyzed by the enzyme alanine decarboxylase AlaDC [106]. Alanine and acetaldehyde can be precursors of ethylamine in plant tissues [107, 108], while alanine precedes acetaldehyde in biosynthetic pathways [109]. Although the key genes for L-theanine biosynthesis are known, their transcriptional regulation remains poorly understood [110]. More than 90 transcription factors from the *AP2-EREBP*, *bHLH*, *C2H2* and *WRKY*, *bZIP*, *C3H*, *MADS*, and *REM* families have recently been found to be involved in the regulation of L-theanine biosynthesis [57]. According to P. Li et al. [88], the transcription factor genes *CsMYB9* and *CsMYB49* are involved in the control of L-theanine biosynthesis, and the expression of the transcription factor gene *CsMYB73* negatively correlated with the accumulation of L-theanine during leaf maturation. In tobacco leaves, the *CsMYB73* gene product binds to the promoter regions of the *CsGS1* and *CsGS2* genes and suppresses their transcription [110]. In addition, the transcription factor *CsWRKY40* activated the key gene for L-theanine hydrolysis, *CsPDX2.1* (pyridoxal-5'-phosphate synthase). Upon wilting and loss of moisture, abscisic acid accumulated in the leaves, and the content of L-theanine decreased against the background of activation of *CsWRKY40* and *CsPDX2.1* expression [111].

Thus, a total of 339 transcription factors belonging to 35 families are involved in the regulation of the biosynthesis of catechins, caffeine, and L-theanine, which determine the quality of the resulting plant production of *C. sinensis* [57]. It is important to note the presence of 67 common transcription factors in the regulatory networks for catechin and caffeine biosynthesis [57]. This indicates a positive correlation between their accumulation [57], which is of interest both from the point of view of the fundamental mechanisms of plant secondary metabolism and for solving practical problems of breeding and optimizing crop cultivation technologies. On the contrary, only two transcription factors turned out to be common in the regulation of the expression of genes for the biosynthesis of catechins and L-theanine, which confirms the inverse relationship between their production in the plant. The fact that the activity of genes responsible for the biosynthesis of catechins, caffeine, and L-theanine is influenced by transcription factors from different families indicates a complex system of transcriptional control during

the formation of the considered biologically active secondary metabolites.

Biosynthesis of secondary metabolites under abiotic stress. Stressful environmental conditions significantly change the content of catechins, caffeine and L-theanine in tea plants [112, 113]. Transcriptomic studies have identified key transcription factors involved in the response to abiotic stress in the tea plant [44, 114-116]. It has been established that many families of transcription factors (*CBF*, *bHLH*, *WRKY*) are involved in responses to various abiotic stresses (cold, drought, salinity), that is, they are nonspecific [117-121].

The summer bud of tea plants reduced the content of catechins and suppressed the expression of the *ANS* gene [122], while the functional activity of the genes for chalcone synthase (*CHS*), flavonoid 3'-hydroxylase (*F3'H*), and dihydroflavonol-4-reductase (*DFR*,) did not change [52]. Increasing the level of illumination during the cultivation of tea calli in vitro contributed to the accumulation of catechins [123]. Short-term (30 min) exposure to ultraviolet (UV-B) irradiation of one-year vegetatively propagated seedlings of *C. sinensis* cvs Yulan and Fudingdabai in pot culture increased, while prolonged (360 min) exposure, on the contrary, decreased the content of catechins [124].

The accumulation of catechins also depended on the water status of plants and fertilizer application [125-127], carbon access and hormonal balance [78]. Thus, with prolonged exposure to drought, a short-term decrease and then an increase in the expression of *CHS*, *DFR*, *LAR*, *ANS*, and *ANR* genes was noted, which correlated with the accumulation of epicatechin gallate, epigallocatechin gallate, and galocatechin gallate [128, 129]. A decrease in the content of polyphenols in tea leaves during drought has been reported [125, 130]. However, under conditions of short-term drought (2 days), the level of expression of the *FLS* and *FNS* genes increased, which was accompanied by an increase in the accumulation of compounds from the flavonoid group [128]. In the tea plant, the activity of the main identified caffeine biosynthesis genes was suppressed in response to drought [128], and the caffeine content in the 3-leaf flush decreased (by 1% on average) compared with the normal moisture content of plants [23, 30]. It was reported [128] that the content of L-theanine in the leaves of *C. sinensis* and the level of expression of the *GOGAT*, *GDH*, *ADC*, and *TS* genes decrease during drought, while the expression of the *ThYD* (L-theanine hydrolase) gene, which encodes the key enzyme of L-theanine degradation, rose.

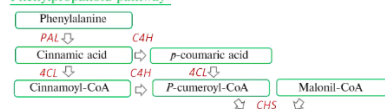
Under nitrogen starvation, the *AlaDC* gene (annotated as a serine decarboxylase gene) was identified in two tea varieties, which may play a specific role in the accumulation of L-theanine [128, 131]. Nitrogen is known to be one of the most important elements for the biosynthesis of L-theanine, caffeine and catechins [38, 132-134]. When nitrogen was deficient, tea plants accumulated various flavonoids, while the synthesis of amino acids, including L-theanine, significantly increased when nitrogen was supplied with this element [62, 135]. The total content of catechins also significantly depended on the amount and ratio of available forms of nitrogen, phosphorus and potassium in the soil [136]. At the same time, the accumulation of simple catechins (epigallocatechin, epicatechin, galocatechin, and catechin) correlated inversely with the amount of N, P, and K introduced into the soil, while their gallic forms directly correlated with the doses of P and K [136]. It has also been reported that elevated doses of phosphorus and potassium, which led to the accumulation of catechins and carbohydrates in tea shoots, reduced the relative content of free amino acids, in particular L-theanine and glutamic acid [137].

Transcription factors and metabolic genes involved in the biosynthesis of catechins, caffeine and L-theanine in the tea plant are shown in the figure.

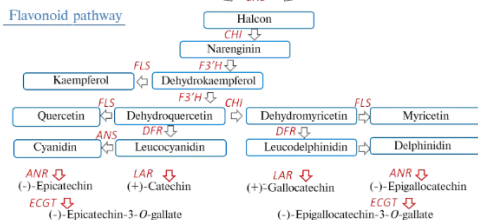
Biosynthesis of catechins

Regulatory genes:
MYB8, MYB89, MYB23, bHLH96, NAC8 et al.

Phenylpropanoid pathway

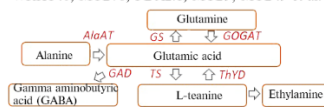


Flavonoid pathway



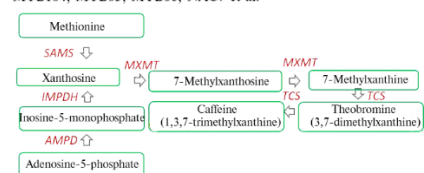
Biosynthesis of L-theanine

Regulatory genes:
WRKY40, MYB78, PDX2.1, MYB9, MYB49 et al.



Biosynthesis of caffeine

Regulatory genes:
MYB184, MYB85, MYB86, NAC7 et al.



Transcription factors and genes for the biosynthesis of catechins, caffeine, and L-theanine in the tea plant *Camellia sinensis* (L.) Kuntze summarised in this review.

So, in recent years, the main metabolic genes involved in the biosynthesis of catechins, caffeine, and L-theanine in the tea plant and their role in the cascade of biochemical reactions have been identified, and some transcription factors involved in the regulation of the expression of these genes have been identified. It is assumed that the identified transcription factors may be associated with the regulators of stress responses, in particular, through the response pathway mediated by abscisic acid. However, there is still insufficient knowledge about the functional role of the regulators of catechin biosynthesis, caffeine, and L-theanine in relation to the key transcription factors of stress responses. This direction seems promising for further research.

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