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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.

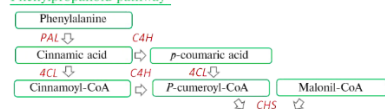
Under nitrogen starvation, the *AlaDC* gene (annotated as a serine decarboxylase gene) was identified in two tea varieties, which may play a specific role in the accumulation of L-theanine [128, 131]. Nitrogen is known to be one of the most important elements for the biosynthesis of L-theanine, caffeine 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.

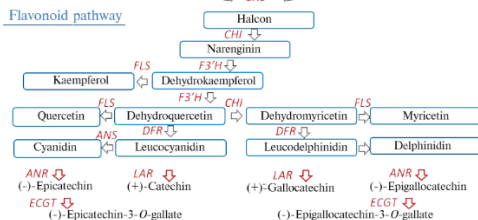
Biosynthesis of catechins

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

Phenylpropanoid pathway

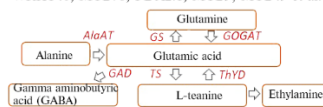


Flavonoid pathway



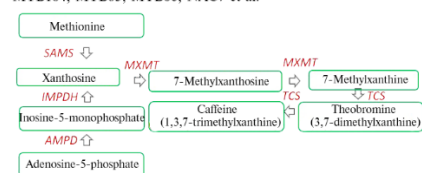
Biosynthesis of L-theanine

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.

REFERENCES

- Zhao J., Li P., Xia T., Wan X. Exploring plant metabolic genomics: chemical diversity, metabolic complexity in the biosynthesis and transport of specialized metabolites with the tea plant as a model. *Crit. Rev. Biotechnol.*, 2020, 40(5): 667-688 (doi: 10.1080/07388551.2020.1752617).
- Sharangi A.B. Medicinal and therapeutic potentialities of tea (*Camellia sinensis* L.) — a review. *Food Research International*, 2009, 42 (5-6): 529-535 (doi: 10.1016/j.foodres.2009.01.007).
- Frei B., Higdon J.V. Antioxidant activity of tea polyphenols *in vivo*: evidence from animal studies. *Journal of Nutrition*, 2003, 133(10): 3275-3284 (doi: 10.1093/jn/133.10.3275S).
- Boschmann M., Thielecke, F. The effects of epigallocatechin-3-gallate on thermogenesis and fat oxidation in obese men: a pilot study. *Journal of the American College of Nutrition*, 2007, 26(4): 389-395 (doi: 10.1080/07315724.2007.10719627).
- Khan N., Mukhtar H. Tea polyphenols for health promotion. *Life Sciences*, 2007, 81(7): 519-533 (doi: 10.1016/j.lfs.2007.06.011).
- Velayutham P., Babu A., Liu D. Green tea catechins and cardiovascular health: An update. *Current medicinal chemistry*, 2008, 15(18): 1840-1850 (doi: 10.2174/092986708785132979).
- Lorenzo J.M., Munekata P.E.S. Phenolic compounds of green tea: health benefits and technological application in food. *Asian Pacific Journal of Tropical Biomedicine*, 2016, 6(8): 709-719 (doi: 10.1016/j.apjtb.2016.06.010).
- Yan Z., Zhong Y., Duan Y., Chen Q., Li F. Antioxidant mechanism of tea polyphenols and its impact on health benefits. *Animal Nutrition*, 2020, 6(2): 115-123 (doi: 10.1016/j.aninu.2020.01.001).
- Vuong Q.V., Bowyer M.C., Roach P.D. L-Theanine: properties, synthesis and isolation from tea. *Journal of the Science of Food and Agriculture*, 2011, 91(11): 1931-1939 (doi: 10.1002/jsfa.4373).
- Khalesi S., Sun J., Buys N., Jamshidi A., Nikbakht-Nasrabadi E., Khosravi-boroujeni H. Green tea catechins and blood pressure: a systematic review and meta-analysis of randomized controlled trials. *European Journal of Nutrition*, 2014, 53(6): 1299-1311 (doi: 10.1007/s00394-014-0720-1).
- Karuppusamy S. A review on trends in production of secondary metabolites from higher plants by *in vitro* tissue, organ and cell cultures. *Journal of Medicinal Plants Research*, 2009, 3(13): 1222-1239 (doi: 10.5897/JMPR.9000026).
- Gaurav N., Juyal P., Tyagi M., Chauhan N., Kumar A. A review on *in vitro* propagation of medicinal plants. *Journal of Pharmacognosy and Phytochemistry*, 2018, 7(6): 2228-2231.
- Zhang X.B. Differences of polyphenols content in Anxi TieGuanYin tea among different seasons and relationship between polyphenols and tea quality. *Agricultural Science & Technology*, 2014,

- 15(7): 1191-1195.
14. Fang R., Redfern S.P., Kirkup D., Porter E.A., Kite G.C., Terry L.A., Berry M.J., Simmonds M.S.J. Variation of theanine, phenolic, and methylxanthine compounds in 21 cultivars of *Camellia sinensis* harvested in different seasons. *Food Chemistry*, 2017, 220: 517-526 (doi: 10.1016/j.foodchem.2016.09.047).
 15. Owuor P.O., Kamau D.M., Jondiko E.O. The influence of geographical area of production and nitrogenous fertilizer on yields and quality parameters of clonal tea. *Journal of Food, Agriculture and Environment*, 2010, 8: 682-690 (doi: 10.20425/IJTS14116).
 16. Malyukova L.S., Tsyupko T.G., Pritula Z.V., Voronova O.B., Gushchaeva K.S., Velikiy A.V. V sbornike: *Fenol'nye soedineniya: funktsional'naya rol' v rasteniyakh* [In: Phenolic compounds: functional role in plants]. Moscow, 2018: 272-277 (in Russ.).
 17. Belous O.G., Platonova N.B. Biologically active substances of *Samellia sinensis* in a humid subtropical climate of Russia. *Slovak Journal of Food Sciences*, 2021, 15: 360-368 (doi: 10.5219/1440).
 18. Gushchaeva K.S., Tsyupko T.G., Voronova O.B., Malyukova L.S. *Zavodskaya laboratoriya. Diagnostika materialov*, 2021, 87(9): 12-19 (doi: 10.26896/1028-6861-2021-87-9-12-19) (in Russ.).
 19. Ercisli S., Orhan E., Ozdemir O., Sengul M., Gungor N. Seasonal variation of total phenolic, antioxidant activity, plant nutritional elements and fatty acids in tea leaves (*Camellia sinensis* var. *sinensis* clone Derepazari 7) grown in Turkey. *Pharmaceutical Biology*, 2008, 46(10-11): 683-687 (doi: 10.1080/13880200802215818).
 20. Lee L.-S., Kim S.-H., Kim Y.-B., Kim Y.-C. Quantitative analysis of major constituents in green tea with different plucking periods and their antioxidant activity. *Molecules*, 2014, 19(7): 9173-9186 (doi: 10.3390/molecules19079173).
 21. Gong A.D., Lian S.B., Wu N.N., Zhou Y.J., Zhao S.Q., Zhang L.M., Cheng L., Yuan H.Y. Integrated transcriptomics and metabolomics analysis of catechins, caffeine and theanine biosynthesis in tea plant (*Camellia sinensis*) over the course of seasons. *BMC Plant Biology*, 2020, 20(1): 294 (doi: 10.1186/s12870-020-02443-y).
 22. Jamir T. Seasonal variations in antioxidant capacities and phenolic contents of tea leaf extracts. *Asian Journal of Pharmaceutical and Clinical Research*, 2020, 13(4): 108-112 (doi: 10.22159/ajpcr.2020.v13i4.36866).
 23. Belous O.G. Influence of microelements on biochemical parameters of tea. *Potravinarstvo*, 2013, 7(S): 149-152.
 24. Diniz P.H.G.D., Pistonesi M. F., Alvarez M.B., Band B.S.F., Araujo M.C.U. Simplified tea classification based on a reduced chemical composition profile via successive projections algorithm linear discriminant analysis (SPA-LDA). *Journal of Food Composition and Analysis*, 2015, 39: 103-110 (doi: 10.1016/J.JFCA.2014.11.012).
 25. Ryndin A.V., Malyukova L.S., Tsyupko T.G., Voronova O.B., Gushchaeva K.S. *Novye tekhnologii*, 2018, 4: 224-229 (in Russ.).
 26. Pritula Z.V., Malyukova L.S., Bekhterev V.N. *Plodovodstvo i yagodovodstvo Rossii*, 2019, 59: 92-98 (doi: 10.31676/2073-4948-2019-59-92-98) (in Russ.).
 27. Zubova M.Yu., Nikolaeva T.N., Nechaeva T.L., Malyukova L.S., Zagoskina N.V. *Khimiya rastitel'nogo syr'ya*, 2019, 4: 249-257 (doi: 10.14258/jcprm.2020016065) (in Russ.).
 28. Sabhapandit S., Karak T., Bhuyan L.P., Goswami B.C., Hazarika M. Diversity of catechin in northeast Indian tea cultivars. *The Scientific World Journal*, 2012, 1-8 (doi: 10.1100/2012/485193).
 29. Sari F., Velioglu Y.S. Changes in theanine and caffeine contents of black tea with different rolling methods and processing stages. *European Food Research and Technology*, 2013, 237(2): 229-236 (doi: 10.1007/s00217-013-1984-z).
 30. Pritula Z.V., Bekhterev V.N., Malyukova L.S. *Subtropicheskoe i dekorativnoe sadovodstvo*, 2015, 54: 185-192 (in Russ.).
 31. Runa J., Haerdter R., Gerendás J. Impact of nitrogen supply on carbon/nitrogen allocation: a case study on amino acids and catechins in green tea [*Camellia sinensis* (L.) O. Kuntze] plants. *Plant Biology*, 2010: 12(5): 724-734 (doi: 10.1111/j.1438-8677.2009.00288.x).
 32. Hrishikesh U., Biman K, D., Lingaraj S., Sanjib K. P. Comparative effect of Ca, K, Mn and B on post-drought stress recovery in tea [*Camellia sinensis* (L.) O. Kuntze]. *American Journal of Plant Sciences*, 2012, 3(4): 443-460 (doi: 10.4236/ajps.2012.34054).
 33. Ruan J., Ma L., Shi Y. Potassium management in tea plantations: its uptake by field plants, status in soils, and efficacy on yields and quality of teas in China. *Journal of Plant Nutrition and Soil Science*, 2013, 176(3): 450-459 (doi: 10.1002/jpln.201200175).
 34. Kwach B.O., Owuor P., Kamau D., Msomba S., Uwimana M.A. Variations in the precursors of plain black tea quality parameters due to location of production and nitrogen fertilizer rates in eastern African clonal tea leaves. *Experimental Agriculture*, 2016: 52(2): 266-278 (doi: 10.1017/S0014479715000083).
 35. Malyukova L.S., Pritula Z.V., Kozlova N.V., Veliky A.V., Rogozhina E.V., Kerimzade V.V., Samarina L.S. Effects of calcium-containing natural fertilizer on *Camellia sinensis* (L.) Kuntze. *Bangladesh Journal of Botany*, 2021, 50(1): 179-187 (doi: 10.3329/bjb.v50i1.52686).

36. Hernaendez I., Alegre L., Munne-Bosch S. Enhanced oxidation of flavan-3-ols and proanthocyanidin accumulation in water-stressed tea plants. *Phytochemistry*, 2006, 67(11): 1120-1126 (doi: 10.1016/j.phytochem.2006.04.002).
37. Xu Z., Zhou G., Shimizu H. Plant responses to drought and rewatering. *Plant Signaling & Behavior*, 2010, 5(6): 649-654 (doi: 10.4161/psb.5.6.11398).
38. Maritim T.K., Kamunya S.M., Mireji P., Mwendia C.M., Muoki R.C., Cheruiyot E.K., Wachira F.N. Physiological and biochemical response of tea (*Camellia sinensis* (L.) O. Kuntze) to water-deficit stress. *The Journal of Horticultural Science and Biotechnology*, 2015, 90(4): 395-400 (doi: 10.1080/14620316.2015.11513200).
39. Samarina L.S., Bobrovskikh A.V., Doroshkov A.V., Malyukova L.S., Matskiv A.O., Rakhmangulov R.S., Koninskaya N.G., Malyarovskaya V.I., Tong W., Xia E, Manakhova K.M., Ryndin A.V., Orlov Y.L. Comparative expression analysis of stress-inducible candidate genes in response to cold and drought of tea plant (*Camellia sinensis* (L.) Kuntze). *Frontiers in Genetics*, 2020, 11: 1613 (doi: 10.3389/fgene.2020.611283).
40. Agati G., Tattini M. Multiple functional roles of flavonoids in photo protection. *New Phytologist*, 2010, 186(4): 786-793 (doi: 10.1111/j.1469-8137.2010.03269.x).
41. Wang Y.S., Gao L.P., Wang Z.R., Liu Y.J., Sun M., Yang D., Wei C., Shan Y., Xia T. Light-induced expression of genes involved in phenylpropanoid biosynthetic pathways in callus of tea (*Camellia sinensis* (L.) O. Kuntze). *Scientia Horticulturae*, 2012, 133: 72-83 (doi: 10.1016/J.SCI-ENTA.2011.10.017).
42. Malyukova L.S., Samarina L.S., Koninskaya N.G., Pritula Z.V., Gvasaliya M.V., Tsyupko T.G., Voronova O.B. *AgroEkoInfo*, 2019, 4: 30 (in Russ.).
43. Malyukova L.S., Nechaeva T.L., Zubova M.Yu., Gvasaliya M.V., Koninskaya N.G., Zagoskina N.V. Physiological and biochemical characterization of tea (*Camellia sinensis* L.) microshoots in vitro: the norm, osmotic stress, and effects of calcium. *Sel'skokhozyaistvennaya biologiya [Agricultural Biology]*, 2020, 55(5): 970-980 (doi: 10.15389/agrobiology.2020.5.970eng).
44. Samarina L., Matskiv A., Simonyan T., Koninskaya N., Malyarovskaya V., Gvasaliya M., Malyukova L., Mytdyeva A., Martinez-Montero M., Choudhary R., Ryndin A. Biochemical and genetic responses of tea (*Camellia sinensis* (L.) Kuntze) microplants under the mannitol-induced osmotic stress in vitro. *Plants*, 2020, 9(12): 1795 (doi: 10.3390/plants9121795).
45. Peng P., Xie Q., Li P., Hou Y., Hu X., Lin, Q. Studies on the allelopathy components of tea. *Southwest China Journal of Agricultural Sciences*, 2009, 22(1): 67-70.
46. Zeng L., Zhou X., Liao Y., Yang Z. Roles of specialized metabolites in biological function and environmental adaptability of tea plant (*Camellia sinensis*) as a metabolite studying model. *Journal of Advanced Research*, 2021, 34: 159-171 (doi: 10.1016/j.jare.2020.11.004).
47. Lillo C., Lea U., Ruoff P. Nutrient depletion as a key factor for manipulating gene expression and product formation in different branches of the flavonoid pathway. *Plant Cell Environ.*, 2008, 31(5): 587-601 (doi: 10.1111/j.1365-3040.2007.01748.x).
48. Akola R., Ravishankar G.A. Influence of abiotic stress signals on secondary metabolites in plants. *Plant Signaling & Behavior*, 2011, 6(11): 1720-1731 (doi: 0.4161/psb.6.11.17613).
49. Xiong L.G., Lia J., Lia Y.H., Yuan L., Liu S., Huang J., Liu Z. Dynamic changes in catechin levels and catechin biosynthesis-related gene expression in albino tea plants (*Camellia sinensis* L.). *Plant Physiology and Biochemistry*, 2013, 71: 132-143 (doi: 10.1016/j.plaphy.2013.06.019).
50. Hong G.J., Wang J., Zhang Y., Hochstetter D., Zhang S., Pan Y., Shi Y., Xu P., Wang Y. Biosynthesis of catechin components is differentially regulated in dark-treated tea (*Camellia sinensis* L.). *Plant physiology and biochemistry*, 2014, 78: 49-52 (doi: 10.1016/j.plaphy.2014.02.017).
51. Lin S., Chen Z., Chen T., Deng W., Wan X., Zhang Z. Theanine metabolism and transport in tea plants (*Camellia sinensis* L.): advances and perspectives. *Critical Reviews in Biotechnology*, 2022, 1-15 (doi: 10.1080/07388551.2022.2036692).
52. Eungwanichayapant P.D., Popluechai S. Accumulation of catechins in tea in relation to accumulation of mRNA from genes involved in catechin biosynthesis. *Plant Physiology and Biochemistry*, 2009, 47(2): 94-97 (doi: 10.1016/j.plaphy.2008.11.002).
53. Jia S., Wang Y., Hu J., Ding Z., Liang Q., Zhang Y., Wang H. Mineral and metabolic profiles in tea leaves and flowers during flower development. *Plant Physiology and Biochemistry*, 2016, 106: 316-326 (doi: 10.1016/j.plaphy.2016.06.013).
54. Bai P., Wei K., Wang L., Zhang F., Ruan L., Li H., Liyun Wu., Cheng H. Identification of a novel gene encoding the specialized alanine decarboxylase in tea (*Camellia sinensis*). *Molecules*, 2019, 24(3): 540 (doi: 10.3390/molecules24030540).
55. Liao Y., Zhou X., Zeng L. How does tea (*Camellia sinensis*) produce specialized metabolites which determine its unique quality and function: a review. *Critical Reviews in Food Science and Nutrition*, 2022, 62(14): 3751-3767 (doi: 10.1080/10408398.2020.1868970).
56. Shi C.Y., Yang H., Wei C.L., Yu O., Zhang Z.Z., Jiang C. J., Sun J., Li Y.Y., Chen Q., Xia T., Wan X.C. Deep sequencing of the *Camellia sinensis* transcriptome revealed candidate genes for major metabolic pathways of tea-specific compounds. *BMC Genomics*, 2011, 12(1): 131 (doi:

- 10.1186/1471-2164-12-131).
57. Li C.-F., Zhu Y., Yu Y., Zhao Q.-Y., Wang S.-J., Wang X.-C., Yao M.-Z., Luo D., Li X., Chen L., Yang Y.-J. Global transcriptome and gene regulation network for secondary metabolite biosynthesis of tea plant (*Camellia sinensis*). *BMC Genomics*, 2015, 16(1): 560 (doi: 10.1186/s12864-015-1773-0).
 58. Wei C., Yang H., Wang S., Zhao J., Liu C., Gao L., Xia E., Lu Y., Tai Y., She G., Sun J., Cao H., Tong W., Gao Q., Li Y., Deng W., Jiang X., Wang W., Chen Q., Zhang Sh., Li Y., Wu J., Wang P., Li P., Shi Ch., Zheng F., Jian J., Huang B., Shan D., Shi M., Fang C., Yue Y., Li F., Li D., Wei Sh., Han B., Jiang Ch., Yin Y., Xia T., Zhang Z., Bennetzen J.L., Zhao Sh., Wan X. Draft genome sequence of *Camellia sinensis* var. *sinensis* provides insights into the evolution of the tea genome and tea quality. *Proceedings of the National Academy of Sciences*, 2018, 115(18): E4151-E4158 (doi: 10.1073/pnas.1719622115).
 59. Li Y., Wang X., Ban Q., Zhu X., Jiang C., Wei C., Bennetzen J.L. Comparative transcriptomic analysis reveals gene expression associated with cold adaptation in the tea plant *Camellia sinensis*. *BMC Genomics*, 2019, 20(1): 624. (doi: 10.1186/s12864-019-5988-3).
 60. Xia E.H., Li F.D., Tong W., Li P.H., Wu Q., Zhao H.J., Ge R.H., Li R.P., Li Y.Y., Zhang Z.Z., Wei C.L., Wan X.C. Tea plant information archive: a comprehensive genomics and bioinformatics platform for tea plant. *Plant Biotechnology Journal*, 2019, 17(10): 1938-1953 (doi: 10.1111/pbi.13111).
 61. Xia E.H., Tong W., Wu Q., Wei S., Zhao J., Zhang Z. Z., Wei C.L., Wan X. C. Tea plant genomics: achievements, challenges and perspectives. *Horticulture Research*, 2020, 7: 7 (doi: 10.1038/s41438-019-0225-4).
 62. Huang H., Yao Q., Xia E., Gao L. Metabolomics and transcriptomics analyses reveal nitrogen influences on the accumulation of flavonoids and amino acids in young shoots of tea plant (*Camellia sinensis* L.) associated with tea flavor. *Journal of agricultural and food chemistry*, 2018, 66(37): 9828-9838 (doi: 10.1021/acs.jafc.8b01995).
 63. Zhen Y.S. Antitumor activity of tea products. In: *Tea: bioactivity and therapeutic potential*. Y.S. Zhen, Z.M. Chen, S.J. Cheng, V.L. Chen (eds.). CRC Press, London. New York, 2002 (doi: 10.1201/b12659).
 64. Guo Q., Zhao B., Shen S., Hou J., Hu J., Xin W. ESR study on the structure-antioxidant activity relationship of tea catechins and their epimers. *Biochimica et Biophysica Acta (BBA)-General Subjects*, 1999, 1427(1): 13-23 (doi: 10.1016/S0304-4165(98)00168-8).
 65. Farkas O., Jakus J., Héberger K. Quantitative structure-antioxidant activity relationships of flavonoid compounds. *Molecules*, 2004, 9(12): 1079-1088 (doi: 10.3390/91201079).
 66. Nakagawa T., Yokozawa T. Direct scavenging of nitric oxide and superoxide by green tea. *Food and chemical Toxicology*, 2002, 40(12): 1745-1750 (doi: 10.1016/s0278-6915(02)00169-2).
 67. Laura A., Moreno-Escamilla J.O., Rodrigo-García J., Alvarez-Parrilla E. *Phenolic compounds. In: Postharvest physiology and biochemistry of fruits and vegetables*. E.M. Yahia (ed.). Woodhead Publishing, 2019 (doi: 10.1016/B978-0-12-813278-4.00012-9).
 68. Alosekh S., Perez de Souza L., Benina M., Fernie A. R. The style and substance of plant flavonoid decoration; towards defining both structure and function. *Phytochemistry*, 2020, 174: 112347 (doi: 10.1016/j.phytochem.2020.112347).
 69. Kamiishi Y., Otani M., Takagi H., Han D.S., Mori S., Tatsuzawa F., Okuhara H., Kobayashi H., Nakano M. Flower color alteration in the liliaceous ornamental *Tricyrtis* sp. by RNA interference mediated suppression of the chalcone synthase gene. *Molecular breeding*, 2012, 30(2): 671-680 (doi: 10.1007/s11032-011-9653-z).
 70. Morita Y., Saito R., Ban Y., Tanikawa N., Kuchitsu K., Ando T., Yoshikawa M., Habu Y., Ozeki Y., Nakayama M. Tandemly arranged chalcone synthase A genes contribute to the spatially regulated expression of siRNA and the natural bicolor floral phenotype in *Petunia hybrida*. *The Plant Journal*, 2012, 70(5): 739-749 (doi: 10.1111/j.1365-313X.2012.04908.x).
 71. Dare A.P., Tomes S., Jones M., McGhie T.K., Stevenson D.E., Johnson R.A., Greenwood D.R., Hellens R.P. Phenotypic changes associated with RNA interference silencing of chalcone synthase in apple (*Malus × domestica*). *The Plant Journal*, 2013, 74(3): 398-410 (doi: 10.1111/tpj.12140).
 72. Jiang C., Schommer C.K., Kim S.Y., Suh D.Y. Cloning and characterization of chalcone synthase from the moss, *Physcomitrella patens*. *Phytochemistry*, 2006, 67(23): 2531-2540 (doi: 10.1016/j.phytochem.2006.09.030).
 73. She H., He S., Zhou Z., Zhang Q. Molecular cloning and sequences analysis of chalcone synthase gene from *Fagopyrum tataricum*. In: *Informatics and management science I*. W. Du (ed.). Springer, London, 2013 (doi: 10.1007/978-1-4471-4802-9_85).
 74. Takeuchi A., Matsumoto S., Hayatsu M. Chalcone synthase from *Camellia sinensis*: isolation of the cDNAs and the organ-specific and sugar-responsive expression of the genes. *Plant and Cell Physiology*, 1994, 35(7): 1011-1018 (doi: 10.1093/oxfordjournals.pcp.a078688).
 75. Mamati G.E., Liang Y., Lu J. Expression of basic genes involved in tea polyphenol synthesis in relation to accumulation of catechins and total tea polyphenols. *Journal of the Science of Food and Agriculture*, 2006, 86(3): 459-464 (doi: 10.1002/jsfa.2368).
 76. Wilmouth R.C., Turnbull J.J., Welford R.W., Clifton I.J., Prescott A.G., Schofield C.J. Structure

- and mechanism of anthocyanidin synthase from *Arabidopsis thaliana*. *Structure*, 2002, 10(1): 93-103 (doi: 10.1016/s0969-2126(01)00695-5).
77. Bogs J., Downey M.O., Harvey J.S., Ashton A.R., Tanner G.J., Robinson S.P. Proanthocyanidin synthesis and expression of genes encoding leucoanthocyanidin reductase and anthocyanidin reductase in developing grapeberries and grapevine leaves. *Plant Physiology*, 2005, 139(2): 652-663 (doi: 10.1104/str.105.064238).
 78. Tanner G.J., Francki K.T., Abrahams S., Watson J.M., Larkin P.J., Ashton A.R. Proanthocyanidin biosynthesis in plants: purification of legume leucoanthocyanidin reductase and molecular cloning of its cDNA. *Journal of Biological Chemistry*, 2003, 278(34): 31647-31656 (doi: 10.1074/jbc.M302783200).
 79. Saito K., Kobayashi M., Gong Z., Tanaka Y., Yamazaki M. Direct evidence for anthocyanidin synthase as a 2-oxoglutarate-dependent oxygenase: molecular cloning and functional expression of cDNA from a red forma of *Perilla frutescens*. *The Plant Journal*, 17(2): 181-189 (doi: 10.1046/j.1365-313x.1999.00365.x).
 80. Punyasin P.A.N., Abeysinghe I.S.B., Kumar V., Treutter D., Duy D., Gosch C., Martens S., Forkmann G., Fischer T.C. Flavonoid biosynthesis in the tea plant *Camellia sinensis*: properties of enzymes of the prominent epicatechin and catechin pathways. *Archives of Biochemistry and Biophysics*, 2004, 431(1): 22-30 (doi: 10.1016/j.abb.2004.08.003).
 81. Xie D.Y., Sharma S.B., Dixon R.A. Anthocyanidin reductases from *Medicago truncatula* and *Arabidopsis thaliana*. *Archives of Biochemistry and Biophysics*, 2004, 422(1): 91-102 (doi: 10.1016/j.abb.2003.12.011).
 82. Zhang L.Q., Wei K., Cheng H., Wang L.Y., Zhang, C.C. Accumulation of catechins and expression of catechin synthetic genes in *Camellia sinensis* at different developmental stages. *Botanical Studies*, 2016, 57(1): 31 (doi: 10.1186/s40529-016-0143-9).
 83. Liu M., Tian H., Wu J., Cang R., Wang R., Qi X., Xu Q., Chen X. Relationship between gene expression and the accumulation of catechin during spring and autumn in tea plants (*Camellia sinensis* L.). *Horticulture Research*, 2015, 2: 15011 (doi: 10.1038/hortres.2015.11).
 84. Nesi N., Jond C., Debeaujon I., Caboche M., Lepiniec L. The *Arabidopsis* TT2 gene encodes an R2R3 MYB domain protein that acts as a key determinant for proanthocyanidin accumulation in developing seed. *The Plant Cell*, 2001, 13(9): 2099-2114 (doi: 10.1105/TPC.010098).
 85. Taylor L.P., Grotewold E. Flavonoids as developmental regulators. *Current Opinion in Plant Biology*, 2005, 8(3): 317-323 (doi: 10.1016/j.pbi.2005.03.005).
 86. Baudry A., Caboche M., Lepiniec L. TT8 controls its own expression in a feedback regulation involving TTG1 and homologous MYB and bHLH factors, allowing a strong and cell-specific accumulation of flavonoids in *Arabidopsis thaliana*. *The Plant Journal*, 2006, 46(5): 768-779 (doi: 10.1111/j.1365-313X.2006.02733.x).
 87. Ravaglia D., Espley R.V., Henry-Kirk R.A., Andreotti S., Ziosi V., Hellens R.P., Costa G., Allan A.C. Transcriptional regulation of flavonoid biosynthesis in nectarine (*Prunus persica*) by a set of R2R3 MYB transcription factors. *BMC Plant Biology*, 2013, 13: 68 (doi: 10.1186/1471-2229-13-68).
 88. Li P., Xia E., Fu J., Xu Y., Zhao X., Tong W., Tang Q., Tadege M., Fernie A.R., Zhao J. Diverse roles of MYB transcription factors in regulating secondary metabolite biosynthesis, shoot development, and stress responses in tea plants (*Camellia sinensis*). *The Plant Journal*, 2022, 110(4): 1144-1165 (doi: 10.1111/tpj.15729).
 89. Song S., Tao Y., Gao L., Liang H., Tang D., Lin J., Wang Y., Gmitter F.G. Jr., Li C. An integrated metabolome and transcriptome analysis reveal the regulation mechanisms of flavonoid biosynthesis in a purple tea plant cultivar. *Frontiers in Plant Science*, 2022, 13: 880227 (doi: 10.3389/fpls.2022.880227).
 90. Mohanpuria P., Kumar V., Yadav S.K. Tea caffeine: metabolism, functions, and reduction strategies. *Food Science and Biotechnology*, 2010, 19(2): 275-287 (doi: 10.1007/s10068-010-0041-y).
 91. Ashihara H., Kubota H. Patterns of adenine metabolism and caffeine biosynthesis in different parts of tea seedlings. *Physiologia Plantarum*, 1986, 68(2): 275-281 (doi: 10.1111/j.1399-3054.1986.tb01926.x).
 92. Negishi O., Ozawa T., Imagawa H. Biosynthesis of caffeine from purine nucleotides in tea plant. *Bioscience, biotechnology, and biochemistry*, 1992, 56(3): 499-503 (doi: 10.1271/bbb.56.499).
 93. Yoneyama N., Morimoto H., Ye C.X., Ashihara H., Mizuno K., Kato M. Substrate specificity of N-methyltransferase involved in purine alkaloids synthesis is dependent upon one amino acid residue of the enzyme. *Molecular Genetics and Genomics*, 2006, 275(2): 125-135 (doi: 10.1007/s00438-005-0070-z).
 94. Ping L., Ren Q., Kang X., Zhang Y., Lin X., Li B., Gao X., Chen Z. Isolation and functional analysis of promoter for N-methyltransferase gene associated with caffeine biosynthesis in tea plants (*Camellia sinensis*). *Journal of Tea Science*, 2018, 38(6): 569-579.
 95. Kato M., Mizuno K., Crozier A., Fujimura T., Ashihara H. Caffeine synthase gene from tea leaves. *Nature*, 2000, 406: 956-957 (doi: 10.1038/35023072).

96. Li P., Ye Z., Fu J., Xu Y., Shen Y., Zhang Y., Tang D., Li P., Zuo H., Tong W., Wang S., Fernie A.R., Zhao J. CsMYB184 regulates caffeine biosynthesis in tea plants. *Plant Biotechnology Journal*, 2022, 20(6): 1012-1014 (doi: 10.1111/pbi.13814).
97. Yamada Y., Sato F. Transcription factors in alkaloid biosynthesis. *International review of cell and molecular biology*, 2013, 305: 339-382 (doi: 10.1016/B978-0-12-407695-2.00008-1).
98. Shi D., Winston J.H., Blackburn M.R., Datta S.K., Hanten G., Kellems R.E. Diverse genetic regulatory motifs required for murine adenosine deaminase gene expression in the placenta. *Journal of Biological Chemistry*, 1997, 272(4): 2334-2341 (doi: 10.1074/jbc.272.4.2334).
99. Zhu B., Chen L.B., Lu M., Zhang J., Han J., Deng W.W., Zhang Z.Z. Caffeine content and related gene expression: novel insight into caffeine metabolism in camellia plants containing low, normal, and high caffeine concentrations. *Agricultural and Food Chemistry*, 2019, 67(12): 3400-3411 (doi: 10.1021/acs.jafc.9b00240).
100. Ma W., Kang X., Liu P., She K., Zhang Y., Lin X., Li B., Chen Z. The *NAC-like* transcription factor CsNAC7 positively regulates the caffeine biosynthesis-related gene *yhNMT1* in *Camellia sinensis*. *Horticulture research*, 2022, 9: uh4046 (doi: 10.1093/hr/uh4046).
101. Hara Y., Luo S.J., Wikramasinghe R.L., Yamanishi T. Special issue on tea. *Food Reviews International*, 1995, 11: 371-545.
102. Harbowy M.E., Balentine D.A., Davies A.P., Cai Y. Tea chemistry. *Critical Reviews in Plant Sciences*, 1997, 16(5): 415-480 (doi: 10.1080/07352689709701956).
103. Thippeswamy R., Mallikarjun Gouda K.G., Rao D.H., Martin A., Gowda L.R. Determination of theanine in commercial tea by liquid chromatography with fluorescence and diode array ultra-violet detection. *Journal of Agricultural and Food Chemistry*, 2006, 54(19): 7014-7019 (doi: 10.1021/jf061715+).
104. Mu W., Zhang T., Jiang B. An overview of biological production of L-theanine. *Biotechnology Advances*, 2015, 33(3-4): 335-342 (doi: 10.1016/j.biotechadv.2015.04.004).
105. Chen Z., Wang Z., Yuan H., He N. From tea leaves to factories: a review of research progress in L-theanine biosynthesis and production. *Journal of Agricultural and Food Chemistry*, 2021, 69(4): 1187-1196 (doi: 10.1021/acs.jafc.0c06694).
106. Lea P.J., Blackwell R.D., Chen F.L., Hecht U. *Enzymes of ammonia assimilation*. In: *Methods in plant biochemistry*. P.J. Lea (ed.). Academic Press, London, 1990 (doi: 10.1016/B978-0-12-461013-2.50022-8).
107. Crocorno O., Fowden L. Amino acid decarboxylases of higher plants: the formation of ethylamine. *Phytochemistry*, 1970, 9(3): 537-540 (doi: 10.1016/S0031-9422(00)85685-X).
108. Smith T. The occurrence, metabolism and functions of amines in plants. *Biological Reviews*, 1971, 46(2): 201-241 (doi: 10.1111/j.1469-185x.1971.tb01182.x).
109. Takeo T. L-Alanine as a precursor of ethylamine in *Camellia sinensis*. *Phytochemistry*, 1974, 13(8): 1401-1406 (doi: 10.1016/0031-9422(74)80299-2).
110. Wen B., Luo Y., Liu D., Zhang X., Peng Z., Wang K., Lia J., Huang J., Liu Zh. The R2R3-MYB transcription factor CsMYB73 negatively regulates L-theanine biosynthesis in tea plants (*Camellia sinensis* L.). *Plant Science*, 2020, 298: 110546 (doi: 10.1016/j.plantsci.2020.110546).
111. Cheng H., Wu W., Liu X., Wang Y., Xu P. Transcription factor CsWRKY40 regulates L-theanine hydrolysis by activating the *CsPDX2.1* promoter in tea leaves during withering. *Horticulture Research*, 2022, 9: uhac025 (doi: 10.1093/hr/uhac025).
112. Duan X., Hu X., Chen F., Deng Z. Bioactive ingredient levels of tea leaves are associated with leaf Al level interactively influenced by acid rain intensity and soil Al supply. *Journal of Food Agriculture and Environment*, 2012, 10: 1197-1204.
113. Ahmed S., Stepp J.R., Orians C., Griffin T., Matyas C., Robbat A., Cash S., Xue D., Long C., Unachukwu U., Buckley S., Small D., Kennelly E. Effects of extreme climate events on tea (*Camellia sinensis*) functional quality validate indigenous farmer knowledge and sensory preferences in tropical China. *PLoS ONE*, 2014, 9(10): e109126 (doi: 10.1371/journal.pone.0109126).
114. Cao H., Wang L., Yue C., Hao X., Wang X., Yang Y. Isolation and expression analysis of 18 CsbZIP genes implicated in abiotic stress responses in the tea plant (*Camellia sinensis*). *Plant Physiology and Biochemistry*, 2015, 97: 432-442 (doi: 10.1016/j.plaphy.2015.10.030).
115. Liu S.-C., Jin J.-Q., Ma J.-Q., Yao M.-J., Ma C.-L., Li C.-F., Ding Z.-T., Chen L. Transcriptional analysis of tea plant responding to drought stress and recovery. *PLoS ONE*, 2016, 11(1): e0147306 (doi: 10.1371/journal.pone.0147306).
116. Chen J., Gao T., Wan S., Zhang Y., Yang J., Yu Y., Wang W. Genome-wide identification, classification and expression analysis of the *HSP* gene superfamily in tea plant (*Camellia sinensis*). *International Journal of Molecular Sciences*, 2018, 19(9): 2633 (doi: 10.3390/ijms19092633).
117. Cui X., Wang Y.X., Liu Z.W., Wang W.L., Li H., Zhuang J. Transcriptome-wide identification and expression profile analysis of the *bHLH* family genes in *Camellia sinensis*. *Functional & Integrative Genomics*, 2018, 18(5): 489-503 (doi: 10.1007/s10142-018-0608-x).
118. Zhu B., Chen L.B., Lu M., Zhang J., Han J., Deng W.W., Zhang Z.Z. Caffeine content and related gene expression: novel insight into caffeine metabolism in *Camellia* plants containing low, normal, and high caffeine concentrations. *Journal of Agricultural and Food Chemistry*, 2019,

- 67(12): 3400-3411 (doi: 10.1021/acs.jafc.9b00240).
119. Hu Z., Ban Q., Hao J., Zhu X., Cheng Y., Mao J., Lin M., Xia E., Li Y. Genome-wide characterization of the C-repeat Binding Factor (CBF) gene family involved in the response to abiotic stresses in tea plant (*Camellia sinensis*). *Frontiers in Plant Science*, 2020, 11: 921 (doi: 10.3389/fpls.2020.00921).
 120. Maritim T., Kamunya S., Mwendia C. Mireji P., Muoki R., Wamalwa M., Francesca S., Schaack S., Kyalo M., Wachira F. Transcriptome-based identification of water-deficit stress responsive genes in the tea plant, *Camellia sinensis*. *Journal of Plant Biotechnology*, 2016, 43(3): 302-310 (doi: 10.5010/JPB.2016.43.3.302).
 121. Parmar R., Seth R., Singh P., Singh G., Kumar S., Sharma R.K. Transcriptional profiling of contrasting genotypes revealed key candidates and nucleotide variations for drought dissection in *Camellia sinensis* (L.) O. Kuntze. *Scientific Reports*, 2019, 9: 7487 (doi: 10.1038/s41598-019-43925-w).
 122. Zhang W.J., Liang Y.R., Zhang F.Z., Chen C.S., Zhang Y.G., Chen R.B., Weng B.Q. Effects on the yield and quality of oolong tea by covering with shading net. *Journal of Tea Science*, 2004, 4: 276-282 (doi: 10.13305/j.cnki.jts.2004.04.010).
 123. Wang R., Zhou W., Jiang X. Reaction kinetics of degradation and epimerization of epigallocatechin gallate (EGCG) in aqueous system over a wide temperature range. *Journal of Agricultural & Food Chemistry*, 2008, 56(8): 2694-2701 (doi: 10.1021/jf0730338).
 124. Zheng X.Q., Jin J., Chen H., Du Y.Y., Ye J.H., Lu J.L., Lin C., Dong J.J., Sun Q.L., Wu L.Y., Liang Y.R. Effect of ultraviolet B irradiation on accumulation of catechins in tea (*Camellia sinensis* (L.) O. Kuntze). *African Journal of Biotechnology*, 2008, 7(18): 3283-3287.
 125. Jeyaramaja P.R., Pius P.K., Kumar R.R., Jayakumar D. Soil moisture stress-induced alterations in bio constituents determining tea quality. *Journal of the Science of Food and Agriculture*, 2003, 83(12): 1187-1191 (doi: 10.1002/jsfa.1440).
 126. Pritula Z.V., Velikiy A.V., Malyukova L.S. *Plodovodstvo i yagodovodstvo Rossii*, 2014, 38(2): 52-58 (in Russ.).
 127. Ding Z., Jia S., Wang Y., Xiao J., Zhang Y. Phosphate stresses affect ionome and metabolome in tea plants. *Plant Physiology and Biochemistry*, 2017, 120: 30-39 (doi: 10.1016/j.plaphy.2017.09.007).
 128. Wang W., Xin H., Wang M., Ma Q., Wang L., Kaleri N.A., Wang Y., Li X. Transcriptomic analysis reveals the molecular mechanisms of drought-stress-induced decreases in *Camellia sinensis* leaf quality. *Frontiers in Plant Science*, 2016, 7: 385 (doi: 10.3389/fpls.2016.00385).
 129. Wang Y.X., Liu Z.W., Wu Z.J., Li H., Zhuang J. Transcriptome-wide identification and expression analysis of the NAC gene family in tea plant [*Camellia sinensis* (L.) O. Kuntze]. *PLoS ONE*, 2016, 11(11): e0166727 (doi: 10.1371/journal.pone.0166727).
 130. Chen X.H., Zhuang C.G., He Y.F., Wang L., Han G.Q., Chen C., He H.Q. Photosynthesis, yield, and chemical composition of Tieguanyin tea plants (*Camellia sinensis* (L.) O. Kuntze) in response to irrigation treatments. *Agricultural Water Management*, 2010, 97(3): 419-425 (doi: 10.1016/j.agwat.2009.10.015).
 131. Bai P., Wei K., Wang L., Zhang F., Ruan L., Li H., Wu L., Cheng H. Identification of a novel gene encoding the specialized alanine decarboxylase in tea (*Camellia sinensis*). *Molecules*, 2019, 24(3): 540 (doi: 10.3390/molecules24030540).
 132. Dong F., Hu J., Shi Y., Liu M., Zhang Q., Ruan J. Effects of nitrogen supply on flavonol glycoside biosynthesis and accumulation in tea leaves (*Camellia sinensis*). *Plant Physiology and Biochemistry*, 2019, 128: 48-57 (doi: https://doi.org/10.1016/j.plaphy.2019.02.017).
 133. Kovalcik J., Klejdus B. Induction of phenolic metabolites and physiological changes in chamomile plants in relation to nitrogen nutrition. *Food chemistry*, 2014, 142: 334-341 (doi: 10.1016/j.foodchem.2013.07.074).
 134. Liu M.Y., Burgos A., Zhang Q., Tang D., Shi Y., Ma L., Yi X., Ruan J. Analyses of transcriptome profiles and selected metabolites unravel the metabolic response to NH₄⁺ and NO₃⁻ as signaling molecules in tea plant (*Camellia sinensis* L.). *Scientia Horticulturae*, 2017, 218: 293-303 (doi: 10.1016/J.SCIENTA.2017.02.036).
 135. Lync J., Jonathan P., Clair S.B.S. Mineral stress: the missing link in understanding how global climate change will affect plants in real world soils. *Field Crops Research*, 2004, 90(1): 101-115 (doi: 10.1016/J.FCR.2004.07.008).
 136. Sun L., Liu Y., Wu L., Liao H. Comprehensive analysis revealed the close relationship between N/P/K status and secondary metabolites in tea leaves. *ACS Omega*, 2019, 4(1): 176-184 (doi: 10.1021/ACSOMEGA.8B02611).
 137. Wei K., Liu M., Shi Y., Zhang H., Ruan J., Zhang Q., Cao M. Metabolomics reveal that the high application of phosphorus and potassium in tea plantation inhibited amino-acid accumulation but promoted metabolism of flavonoid. *Agronomy*, 2022, 12(5): 1086 (doi: 10.3390/agronomy12051086).