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RESEARCH ARTICLE

Development of the Composition and Technology for Producing Green Tea Leaf Extract with Antioxidant Effects based on Theoretical and Practical Research

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ABSTRACT

The aim of the work was to develop the composition and technology for obtaining green tea leaf extract with antioxidant effects based on theoretical and practical research. Theoretical studies of the antioxidant effect were carried out by molecular docking with the AutoDockTools 1.4.6 program, the quantitative content of biologically active substances (BAS) was determined by HPLC-UV, and the level of antioxidant action was studied by the potentiometric method. In in sillico studies, epicatechin, (+)-catechin and epigallocatechin inhibit the active sites of pro-oxidant enzymes more effectively than epigallocatechin-3-O-gallate, epicatechin-3-O-gallate and gallic acid. The level of antioxidant activity of epigallocatechin-3-O-gallate was the highest (), and gallic acid was the lowest (). After hydrolysis of green tea leaf extract, the content of epigallocatechin increased by 46%, epicatechin by 64%, and gallic acid by 91%, while gallic acid esters were not identified. The antioxidant interaction of combinations of gallic acid with epicatechin and with epigallocatechin is antagonistic. During the study, a composition and technology for obtaining green tea leaf extract was developed, including the destruction of esters and the removal of gallic acid.

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1.Introduction

The excess of reactive oxygen species (ROS) and reactive nitrogen species (RNS) cause oxidative damage due to their high reactivity[1]. To ROS can be belong free radicals as the superoxide radical ($O_2^{\cdot-}$), hydroxide ion (HO^-), hydroxyl radical (OH^-), peroxide ion (O_2^{2-}), triplet oxygen (O_2^{2-}), whereas to RNS belong nitric oxide (NO^-)[2]. In the recent researches that indexed in Scopus has been found that the oxidative damage has a central part in the occurrence and development of such diseases as atherosclerosis, Alzheimer's disease, cancer, ischemia and diabetes mellitus.[3]. That is why, there is high demand among population on the herbal medicines and antioxidants, especially nature origin.

Tea (*Camella sinensis L.)* is an over green shrub which mainly grow in China, India and Japan. The main constituents are catechins (15.0-35.0%), flavonols (5.0%), caffeine (1.5-3.5%), organic acids (1.5%), phenolic acids (0.5 – 5%), free amino acids (1-5.5%), carbohydrates (10 – 20%), proteins (5.0 – 10.0%)[4]. The 80% of phenolic compounds has been presented by flavan-3-ols or catechins.

Epigallocatechin-3-O-gallate and epicatechin-3-O-gallate are one of the main catechin derivatives in green tea leaf. Epigallocatechin-3-O-gallate is a 3-position ester of epigallocatechin and gallic acid, and epicatechin-3-O-gallate is an ester of epicatechin and gallic acid (Figure 1). Many journals indexed in the scientometric databases Scopus and Web of Science have shown that Epigallocatechin-3-O-gallate and epicatechin-3-O-gallate have anti-inflammatory[5], anticancer[6], antiviral[7], cardioprotective[8], neuroprotective[9] and antimicrobial[10], as well as antioxidant effects[11]. One of the main ways to obtain green leaf extract with a high content of epigallocatechin-3-O-gallate and epicatechin-3-O-gallate is to carry out extractions with ethanol and subsequent chromatographic purification from non-hallotated catechins. But, in our opinion, the pharmacological effect of gallic acid esters is overestimated in the scientific community for a number of reasons: firstly, epigallocatechin-3-O-gallate and epicatechin-3-O-gallate are unstable compounds and are quickly dislocated to epicatechin or epigallocatechin and gallic acid; the second main reason is the bioavailability of epigallocatechin-3-O-gallate and epicatechin-3-O-gallate, these gallic acid esters have a large molecular weight, and the next important point is the low absorption in the intestine by Caco-2 cells compared to epicatechin and gallic acid[12]. Thus, we believe that green tea leaf extract should contain only epicatechin, (+)-catechin, epigallocatechin and gallic acid, since this combination is more optimal in creating the drug than the use of esters of epicatechin or epigallocatechin and gallic acid.

Thus, the purpose of our research is to develop the optimal composition and technology for producing green tea leaf extract with an antioxidant effect based on catechin derivatives.

2. Materials and methods

2.1 Plant material

Green tea (*Camellia sinensis* L.) leaf was collected in Anhui province, China (30.634140518993203, 116.33254121482477). «»

2.2 Reagents

«Methanol (purchased from «Allchem», Kharkiv), phosphoric acid (purchased from «Allchem», Kharkiv), epigallocatechin-3-O-gallate (≥98.0%), epicatechin-3-O-gallate (≥98.0%), epicatechin (≥98.0%), (+)-catechin (≥98.0%), epigallocatechin (≥98.0%), gallic acid (≥98.0%) were purchased in Sigma Aldrich Company, Lublin, Poland.

2.2 Antioxidant activity assay

«Antioxidant activity of extract was evaluated by potentiometric method[13, 14]. Antioxidant activity was calculated according to the following equation and expressed as mmol-equiv./$m_{dry\ res.}$:

$$AOA = \frac{C_{ox} - \alpha \times C_{red}}{1+\alpha} \times K_{dil} \times 103 \times \frac{m_1}{m_2}$$

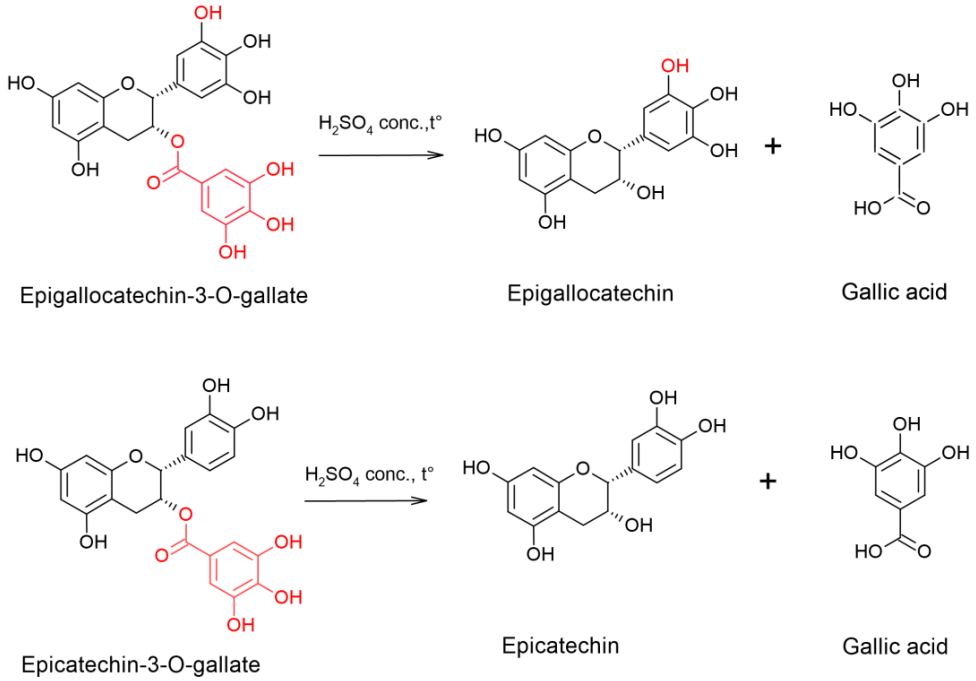


Figure 1. *Acid hydrolysis of epigallocatechin-3-O-gallate and epicatechin-3-O-gallate*

where, $\alpha = C_{ox}/C_{red} \times 10^{(\Delta E - E\text{ethanol})nF/2.3RT}$; C_{ox} : concentration of $K_3[Fe(CN)_6]$, mol/L; C_{red} – concentration of $K_4[Fe(CN)_6]$, mol/L; $E_{ethanol}$: $0.0546 \cdot C_{\%} - 0.0091$; $C_{\%}$: concentration of ethanol; ΔE : change of potential; F = 96485.33 C/mol : Faraday constant; n = 1 – number of electrons in electrode reaction; R = 8.314 J/molK : universal gas constant; T = 298 K; K_{dil} : coefficient of dilution; m_1 : mass of dry residue; m_2 : mass of dry residue in 1.0 mL of extract.

2.3 HPLC analysis of *C. sinensis* leaf extract

«A Prominence LC-20 Shimadzu liquid chromatography system equipped with a Thermo Scientific Syncronis aQ C18 colomn (4.6 × 250) was employed for analyses. All determinations were undertaken at 40 ºC. Mobile phases included an aqueous solution of methanol (A) and 1.0% phosphoric acid solution (B). Gradients of 20–42 % A for 0–15 min, 42–43 % A for 15–25 min, 43–90 % A for 25–45 min, keeping 90 % A for 45–55 min, decreasing to 20% A for 55–60 min, and keeping 20% A for 60–70 were used. The mobile phases were filtered (25mm × 0,45 µm, Supelco Iso-Disc Filters PTFE 25-4) and degassed prior to use, and a flow rate of 0.5 mL/min was employed. The sample injection volume was 5 µmL and the detection was carried out at 255, 286, 350 nm. «

«Chromatographic peaks of analytes were identified by the following similarity indexes, which were calculated between the test substance and the standard according to the formulas:

$$I_T = 1 - |T_{st} - T_u|$$
$$I_{255} = 1 - |h_{255_{st}} - h_{255_u}|$$
$$I_{286} = 1 - |h_{286_{st}} - h_{286_u}|$$
$$I_{350} = 1 - |h_{350_{st}} - h_{350_u}|$$

where, I_T – retention time similarity index, T_{st} – retention time of standard (min), T_u – test substance retention time (min), I_{255}, I_{286} and I_{350} – spectral similarity indices, h_{255st}, h_{286st} and h_{350st} – spectral characteristics of the standard, h_{255u}, h_{286u} and h_{350u} – spectral characteristics of the test substance.

The smallest of the three values of the similarity index of spectral characteristics determines the degree of similarity I_L substances and standards

for these characteristics. The higher value of the I_L, the more likely it will be more accurately identify the substance. Substances, which had the degree of similarity of which with the catechin standard was not less than 0.7 and the peaks of these substances on the chromatogram were located in the range between the peak of catechin and the earliest peak of flavonoids, were identified as catechins[15].

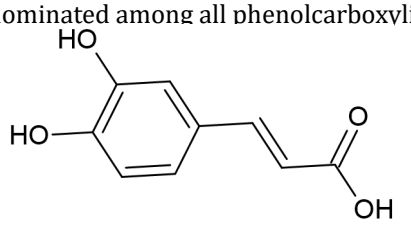
2.4 Molecular docking

A molecular docking study was conducted using the tool known as AutoDockTools 1.5.6. The preparation of the protein involved an optimization process, which included the removal of water and other atoms, followed by the addition of a polar hydrogen group. Autogrid was used to configure the grid coordinates (X, Y, and Z) on the binding site. Genetic algorithm parameters were applied for ligand interaction, with 10 runs of this criterion.

Myeloperoxidase (PDB: 3f9p), xanthine oxidase (PDB: 1fiq), NADPH oxidase (PDB ID: 5o0X) structures were obtained from PDB database[16]. The resolution of 5o0X – 2.20 Å, 3f9p – 2.93 Å, 1fiq – 2.50 Å. For docking experiment protein structure is selected if resolution above 2 Å. So, all mentioned proteins can be used for the experiment. The ligand structures of epigallocatechin-3-O-gallate (CID_ 65064), gallic acid (CID_370), epicatechin (CID_72276), (+)-catechin (CID_9064) were obtained from PubChem database[17]. The active site of the docking protein was identified utilizing the Computed Atlas for Surface Topography of Proteins (CASTp)[18].

3. Results

In our previous work, the content of catechins and phenolcarboxylic acids in green tea leaf was studied by HPLC-UV[19]. Based on the results, it was found that green tea leaves contain (+)-catechin, epicatechin, epigallocatechin, epicatechin-3-O-gallate, epigallocatechin-3-O-gallate, gallic and caffeic acid (Fig. 2). The leader among all catechin derivatives was epigallocatechin-3-O-gallate, the second place was occupied by epicatechin-3-O-gallate, and caffeic acid dominated among all phenolcarboxylic acids.



Caffeic acid

Figure 2. *Chemical structure of identified compounds in green tea leaf by HPLC-UV*

To understand the possibilities and differences in the pharmacological activity of gallic acid esters, epicatechin, and epigallocatechin, we theoretically assessed the antioxidant activity by molecular docking against pro-oxidant enzyme structures: NADPH oxidase, myeloperoxidase and xanthioxidase.

The active site of NADPH oxidase consisted of the following amino acids: Glu691. Ser522. Glu443. Thr462. Cys668. Phe667. Pro521. Thr520. Tyr445. Pro542. Asp444. Phe693. According to the results obtained, it was found that epigallocatechin had the highest affinity for the active site, second place was occupied by (±)-catechin, and gallic acid had the worst binding energy. By comparing the binding energies of gallic acid esters and their corresponding tandems of gallic acid and epicatechin or epigallocatechin, it was found that in the case of epicatechin-3-O-gallate, the affinity level of epicatechin was 10% higher, and the binding energy of gallic acid was 20% lower . When comparing the results of theoretical studies of epigallocatechin-3-O-gallate, gallic acid and epigallocatechin, it was shown that the affinity of epigallocatechin for the active site was 21% higher than that of epigallocatechin-3-O-gallate, and the binding energy of gallic acid was by 19% lower.

The next important pro-oxidant enzyme that has been studied is myeloperoxidase. The active center of the enzyme is represented by the following amino acids: Leu420, Pro145, Arg42, Met411, Ile9, Leu425, Arg333, Leu417, Phe146. In Table. Figure 1 shows that (+)-catechin binds most effectively to the active center of the enzyme, epicatechin is in second place, and gallic acid inhibits this enzyme least of all. Com-

Table 1. Results of molecular docking of (+)-catechin, epicatechin, gallic acid, epigallocatechin and epigallocatechin-3-O-gallate with the NADPH oxidase, myeloperoxidase, xanthine oxidase structures

№	Ligand	NADPH oxidase	№	Ligand	Myeloperoxidase	№	Ligand	Xanthine oxidase
		ΔGbind[a] (kcal/mol)			ΔGbind[a] (kcal/mol)			ΔGbind[a] (kcal/mol)
1	Epigallocatechin	-7.57	1	(+)-catechin	-5.57	1	(+)-catechin	-7.43
2	(+)-catechin	-7.15	2	Epicatechin	-5.04	2	**Epigallocatechin-3-O-gallate**	**-7.30**
3	Epicatechin	-7.11	3	Epigallocatechin	-4.96	3	**Epicatechin-3-O-gallate**	**-7.25**
4	**Epigallocatechin-3-O-gallate**	**-5.97**	4	**Epigallocatechin-3-O-gallate**	**-4.52**	4	Epicatechin	-7.21
5	**Epicatechin-3-O-gallate**	**-5.87**	5	**Epicatechin-3-O-gallate**	**--4.48**	5	Epigallocatechin	-6.93
6	Gallic acid	-4.86	6	Gallic acid	-4.41	6	Gallic acid	-4.86

Notes: a – free-binding energy

paring epigallocatechin-3-O-gallate with gallic acid and epigallocatechin, it was found that epigallocatechin inhibited the enzyme 9% more actively than epigallocatechin-3-O-gallate, and gallic acid inhibited 2% less. Carrying out a comparative analysis of the second ester of epicatechin-3-O-gallate with gallic acid and epicatechin, it was found that the binding energy of epicatechin was 11% higher than its corresponding ester, and gallic acid inhibited the enzyme 2% worse.

The last enzyme that has been theoretically studied with compounds is xanthioxidase. The active site of xanthine oxidase is represented by the following amino acids: Ala255. Leu257. Glu402. Leu398, Pro400. Thr396. Gly399. Lys256. Ile403. Lys249. According to the research results shown in Table. 1 it was shown that (+)-catechin binds most actively to the active site, and gallic acid has the least ability to inhibit xanthine oxidase. When comparing the binding energies of epicatechin-3-O-gallate ester with gallic acid and epicatechin, it was found that epicatechin was slightly inferior to epicatechin-3-O-gallate by 1%, and the level of binding of gallic acid was lower by 33%. Comparing epigallocatechin-3-O-gallate with gallic acid and epigallocatechin, it was shown that epigallocatechin inhibited the active site of the enzyme by 5% lower than epigallocatechin-3-O-gallate, and in the case of gallic acid - by 33%.

The antioxidant activity of model solutions of (+)-catechin, epicatechin, gallic acid, epicatechin-3-O-gallate, epigallocatechin-3-O-gallate with a molar concentration of 0.1 M was studied using the potentiometric method. Based on the data obtained, it was established that the level of antioxidant activity of the above compounds increases in the following order gallic acid (61.7 mmol-equiv./L) < epicatechin=(+)-catechin (78.9 mmol-equiv./L) < epigallocatechin (81.0 mmol-equiv./L) < epicatechin-3- O-gallate (84.4 mmol-equiv./L) < epigallocatechin-3-O-gallate (85.5 mmol-equiv./L).

The next stage of our experimental work was to study the antioxidant effect of model solutions of gallic acid esters and combinations of gallic acid with epicatechin and epigallocatechin. As a result of the obtained data shown in Table 1. It was found that the level of antioxidant effect of epicatechin-3-O-gallate was 10% higher, and the model solution of epigallocatechin-3-O-gallate was 15% higher than the solution of combinations of gallic acid and epicatechin, epigallocatechin, respectively.

In the course of our analysis, we found that the experimental value of the level of antioxidant activity of model solutions of gallic acid with epicatechin and epigallocatechin was lower by 40 and 47% than the level of antioxidant activity of the theoretical sum of the level of antioxidant activity of gallic acid with epicatechin and epigallocatechin, respectively.

To understand whether the ester bond of gallic acid and catechins is destroyed, we carried out acid hydrolysis of green tea leaf extract, obtained by dou-

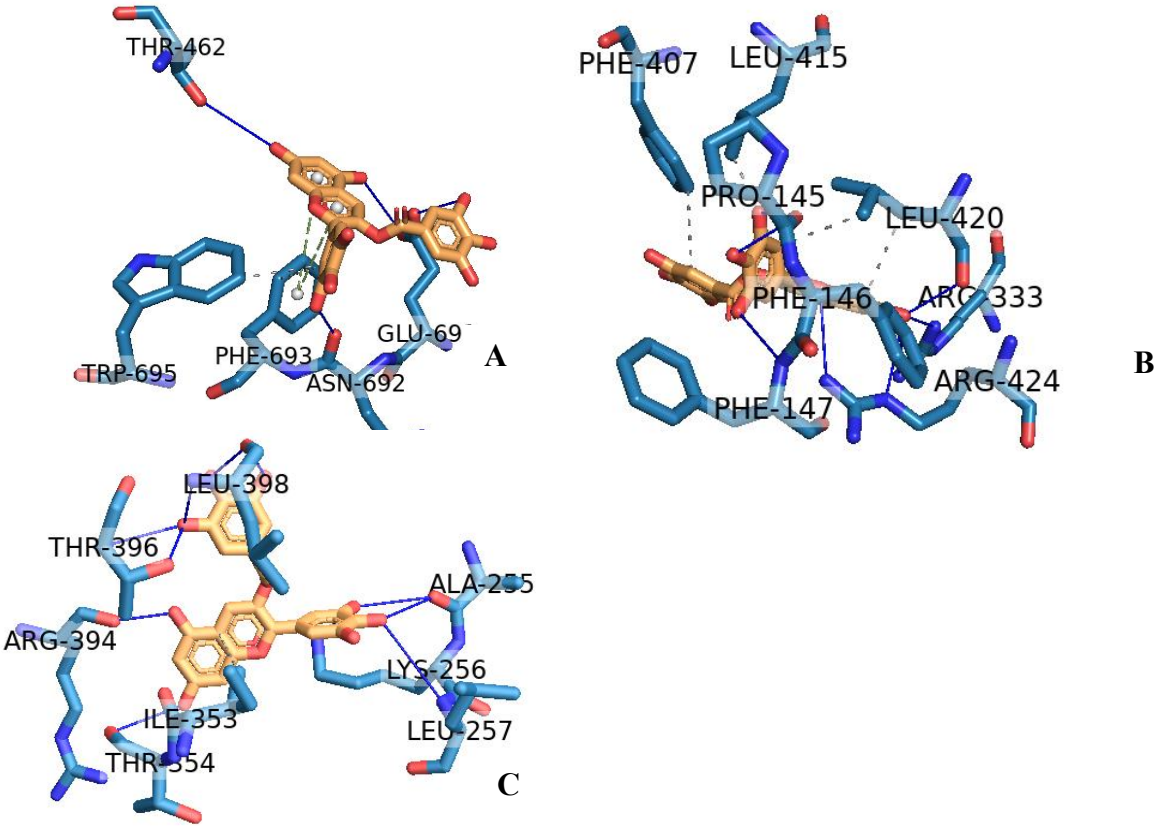


Figure 2. *Molecular interaction analysis of epigallocatechin-3-O-gallate with active center of NADPH oxidase (A), myeloperoxidase (B) and xanthine (C) structures*

Table 2. Results of antioxidant activity of model solutions of epicatechin, gallic acid, epicatechin-3-O-gallate, epigallocatechin, epigallocatechin-3-O-gallate

№	Sample	Molar concentration, mole/L	Antioxidant activity, mmol-equiv./L, ±SD	Theoretical value of antioxidant activity, mmol-equiv./L	Difference,%
1	Epicatechin	0.10	78.9±1.00	**140.6**	**-40%**
2	Gallic acid		61.7±1.00		
3	Epicatechin + Gallic acid		70.0±1.00		
4	**Epicatechin-3-O-gallate**		**84.4±1.00**		
5	Epigallocatechin		81.0±1.00	**142.7**	**-47%**
7	Gallic acid		61.7±1.00		
6	Epigallocatechin + Gallic acid		**76.2±1.00**		
8	**Epigallocatechin-3-O-gallate**		**85.5±1.00**		
9	(+)-catechin		78.9±1.00		

Table 3. Chemical composition of catechins and gallic acid in unhydrolyzed *C. sinensis* leaf extract by HPLC-UV analysis

№	Substances	Content of substances before hydrolysis in the extract	№	Substances	Content of substances after hydrolysis in the extract
1	Epigallocatechin	2760.0±2.00	1	Epigallocatechin	5158±2.00
2	(+)-catechin	210.0±2.00	2	(+)-catechin	210.0±2.00
3	Epicatechin	1010.0±2.00	3	Epicatechin	2768.0±2.00
4	Epigallocatechin-3-O-gallate	3730.0±2.00	4	Gallic acid	2572±2.00
5	Epicatechin-3-O-gallate	2788.0±2.00			
6	Gallic acid	210±2.00			

ble extraction with 96% ethanol in a ratio of 1/20 in a water bath at T = 70º C for 1 hour, evaporated to 1:2 to the mass of raw materials. For hydrolysis, sulfate acid was used, hydrolysis time - 2 hours, at a temperature of 70º C in a water bath. After this, an excess of $BaCO_3$ was added to the extract, then the extract was centrifuged at 4000 rpm, the sediment was collected and quantitatively analyzed by HPLC.

When comparing the quantitative content of biologically active substances in green tea extract without hydrolysis and with hydrolysis, it can be found that after hydrolysis, gallic acid esters were destroyed. As a result, the content of epigallocatechin increased by 46%, epicatechin by 64%, and gallic acid by 91%. (Table 3)

4. Discussion

To develop the composition and technologies for producing green tea extract with antioxidant action, we assessed the theoretical potential of gallic acid esters and epicatechin, epigallocatechin, gallic acid to inhibit pro-oxidant enzymes. When studying the antioxidant effect of the above compounds against the prooxidant enzymes NADPH oxidase and myeloperoxidase, it was found that epicatechin and epigallocatechin inhibit these enzymes better than their gallic acid esters. In the case of the xanthine oxidase enzyme, epigallocatechin-3-O-gallate and epicatechin-3-O-gallate inhibit the active site more effectively than epicatechin and epigallocatechin. But the difference in binding energies is a fraction of a percent, which can be neglected. Also, in the course of theoretical studies, gallic acid showed a low level of binding efficiency with enzymes, which indicates a weak effect of gallic acid on pro-oxidant enzymes.

In experimental studies of the antioxidant activity of model solutions of the studied compounds, it was shown that the level of antioxidant activity increases in the following order: gallic acid < epicatechin=(+)-catechin < epigallocatechin < epicatechin-3-O-gallate < epigallocatechin-3-O-gallate. This obtained dependence can be justified through the values of the standard electrode potential (E0). The standard electrode potential shows the tendency of a substance to oxidize or reduce; the higher the level of this value, the more powerful the oxidizing agent this substance is. In our case, when comparing standard electrode potentials with the test substances, the following order was obtained: epigallocatechin-3-O-gallate (E0=0.253 V) < epicatechin-3-O-gallate (E0=0.260 V) < epigallocatechin < (E0=0.277 B) < epicatechin=(+)-catechin (E0=0.287 V) < gallic acid (E0=0.480 V)[20]. We can see that both orders are comparable to each other, which means that our hypothesis is correct.

Our results revealed that epicatechin and epigallocatechin in combination with gallic acid have an antigonistic interaction. In our opinion, this is due to the fact that epicatechin and epigallocatechin interact with the oxidizing agent first of all, since their E0 is significantly less than gallic acid,

Table 4. Developed technology for obtaining green tea leaf extract with antioxidant effect based on epicatechin and epigallocatechin

Stage	Technology	Explanation
1 stage	Grinding of raw materials (the size of the raw materials should be from 1-2 mm)	With large sizes (>2 mm) of raw materials, the extraction of biologically active substances deteriorates
2 stage	Extraction with 96% ethanol in a ratio of 1/20, in a water bath at T = 70º C for 1 hour, filtration, evaporation to 1:1 mass of raw materials	These extraction conditions are optimal, since with this extraction method more than 80% of the total antioxidant capacity of the raw material is extracted []
3 stage	Acid hydrolysis (H_2SO_4, at T = 70º C for 2 hours)	By hydrolysis, gallic acid esters can be destroyed and gallic acid and catechin monomers can be obtained in the extract.
4 stage	Add excess $BaCO_3$, centrifuge at 4000 rpm, collect supernatant	$BaCO_3$ was used to remove excess sulfuric acid
5 stage	Extraction of the resulting extract with chloroform	To remove gallic acid derivatives, organic acids, chlorophylls.
6 stage	Preparation of Green Tea Leaf Extract	Extract standardization

and after epicatechin and epigallocatechin become pro-oxidants, which will subsequently oxidize gallic acid, which will lead to a decrease in antioxidant properties of gallic acid. We have already observed the antigonistic nature of the interaction when studying the antioxidant activity of combinations of rutin and ascorbic acid in the drug "Ascorutin"[21], the same dependence was found, which indicates the presence of a pattern.

Based on the above theoretical and practical results, the following conclusion can be drawn:

1) green tea extract should contain only catechin monomers, and not their esters with gallic acid. There are a number of reasons for this: firstly, epicatechin and epigallocatechin have better bioavailability than their esters, which is associated with high levels of absorption by Caco-2 cells in the intestine; secondly, according to our theoretical results, gallic acid esters are significantly inferior to epicatechin and epigallocatechin in inhibiting pro-oxidant enzymes;

2) gallic acid must be removed from the extract, since it acts as an antagonist and not a synergist with catechins; Gallic acid also inhibits pro-oxidant enzymes more weakly and has a lower level of antioxidant activity. According to the conclusion made, we have developed the following technology for obtaining green tea leaf extract with antioxidant effects.

The developed technology consists of 6 stages and is presented in Table. 4

5. Conclusion

In *in sillico* studies, epicatechin, (+)-catechin and epigallocatechin were found to inhibit active sites more effectively than epigallocatechin-3-O-gallate, epicatechin-3-O-gallate and gallic acid. The antioxidant interaction of combinations of gallic acid with epicatechin and with epigallocatechin is antagonistic. During the study, a composition and technology for obtaining green tea leaf extract was developed, including the destruction of esters and the removal of gallic acid.

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