

MOLDOVA STATE UNIVERSITY
DOCTORAL SCHOOL OF NATURAL SCIENCES

Consortium: Moldova State University, Institute of Chemistry

As manuscript
C.Z.U.: 502.175:542.943'78:634.86(043)

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**ANTIOXIDANT INTERACTIONS BETWEEN SOME
PHENOLIC COMPOUNDS AND ORGANIC ACIDS
FROM GRAPES – CONTRIBUTION TO THE
ECOVALEOLOGICAL TRAINING OF YOUNG
SPECIALISTS**

145.01 Ecological chemistry

Abstract of the doctoral thesis in chemical sciences

CHISINAU, 2024

The thesis has been developed within the Laboratory of Physical and Quantum Chemistry,
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The public defence of the thesis will take place on **4th of October, 2024**, at **14:00**, at the meeting
of the Doctoral Commission within the Doctoral School of Natural Sciences, MSU. Location –
Moldova State University (<http://www.usm.md>), 65A, M. Kogălniceanu str., study block 3, hall
332, MD-2009, Chisinau, Moldova.

The doctoral thesis and summary can be consulted at the National Library of the Republic of
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(<http://www.usm.md>).

The summary was sent on ”20 ” august _____ 2024

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SUMMARY

CONCEPTUAL FRAMEWORK OF THE RESEARCH.....	4
THESIS CONTENT.....	6
1. MATERIALS AND METHODS USED IN THE STUDY OF ANTIOXIDANT INTERACTIONS.....	6
2. CHARACTERIZATION OF THE CHEMICAL COMPOSITION OF LOCAL GRAPES AT DIFFERENT MATURATION PERIODS.....	7
2.1. Basic and specific physico-chemical indices of local grapes.....	7
2.2. The antioxidant activity of studied grape varieties.....	10
2.3. Establishment of the optimal concentrations of phenolic compounds and organic acids for the study of antioxidant interactions.....	11
3. ANTIOXIDANT INTERACTIONS BETWEEN NATURAL COMPOUNDS FROM GRAPES.....	12
3.1. Antioxidant interactions between grape phenolic compounds and organic acids.....	12
3.2. Antioxidant interactions between grape phenolic compounds and dihydroxyfumaric acid.....	15
3.3. Antioxidant interactions between ascorbic acid and other grape compounds.....	17
3.4. Antioxidant activity of ENOXIL and the antioxidant interactions in the mixture with ascorbic acid.....	22
4. ECOVALEOLOGICAL CONCEPTS DEVELOPMENT AT THE ECOLOGICAL CHEMISTRY DISCIPLINE.....	25
4.1. Relationship between the study of antioxidant interactions and the concept of valeology.....	26
4.2. Development of students' ecovaleological concepts – a sustainable approach in solving ecological problems.....	26
4.3. Integration of the ecovaleology concept into the curriculum of the Ecological Chemistry discipline.....	26
CONCLUSIONS AND RECOMMENDATIONS.....	27
BIBLIOGRAFY and LIST OF PUBLICATIONS ON THE THESIS TOPIC.....	30
ADNOTARE.....	32
ANNOTATION.....	33
АННОТАЦИЯ.....	34

CONCEPTUAL FRAMEWORK OF THE RESEARCH

Actuality and importance of the topic addressed. Antioxidants are compounds that, due to their structural diversity and complexity, and mechanisms of action, have the ability to annihilate reactive species. In accordance with the ecological living conditions appropriate for a healthy life [1], daily exposure to risk factors that generate free radicals makes the intake of antioxidant compounds a necessity for regulation of the balance of redox reactions in the body. The consumption of food products, especially those of vegetable origin, is the main source of antioxidants, along with the consumption of food supplements which are becoming more popular.

The main difference between antioxidants from natural sources and those from dietary supplements consists, (1) in the concentrations of these compounds, which vary considerably from one source to another, and, (2) in the fact that, in nature, antioxidants are in combination with other antioxidant or non-antioxidant compounds – a circumstance that significantly influences the total reducing activity, by generating synergistic, additive or antagonistic antioxidant interactions (IA) [2]. Contrary to this, antioxidants applied individually and in high concentrations, compared to their content in nature, can become prooxidants under certain conditions of pressure, pH, solvent, or in the presence of heavy metals [3], etc.

Grapes are complex natural systems that include an impressive number of organic and inorganic compounds, a large part of them possessing antioxidant activity. Although scientific interest remains focused on compounds with enhanced antioxidant properties, for example: ascorbic acid (AA), dihydroxyfumaric acid (DHF), catechin (Cat), quercetin (Que), rutin (Rut), gallic acid (AG), resveratrol (Res) etc., the presence and influence of non-antioxidant compounds such as tartaric (AT), citric (AC), malic acids is found to be significant for the total antioxidant activity of the mixtures.

Ecovaleology, is a scientific direction that studies the influence of natural factors and consequences of environmental changes caused by anthropogenic actions on human health, as well as defines the nature of human behaviour in different environmental conditions with the aim of maintaining health [4]. Therefore, ecovaleology is the discipline that covers the scientific subjects on the impact of antioxidants on the human health, the effect of their concentration and combination, the risk of prooxidant character, the advantages/disadvantages of consuming food supplements, the benefit of the daily intake of natural antioxidants on the health status of individuals.

The aim of the thesis is to determine the type of antioxidant interactions between some grapes' phenolic compounds and organic acids, and the dependence of antioxidant effects on the

concentration and combination of the investigated substances, followed by the formulation of conclusions regarding the consumption and efficient use of antioxidants.

Objectives characteristic to the purpose of the work are:

- study of the specialized literature on the mechanisms of antioxidant action of natural compounds, the problem of prooxidant character, the types of antioxidant interaction between natural compounds, the antioxidant activity of grapes phenolic and non-phenolic compounds and the study of the concept of ecovaleology as a scientific direction;
- determination of the chemical composition and antioxidant activity of local grape varieties at different ripening periods and the use of experimental and bibliographic data to establish the concentrations of antioxidants – ascorbic acid, gallic acid, catechin, quercetin, rutin, resveratrol, and non-antioxidant compounds – tartaric acid, citric acid, suitable for evaluation of the type of antioxidant interaction;
- investigation of the antioxidant interactions between tartaric, citric or dihydroxyfumaric acids in combination with phenolic compounds (gallic acid, catechin, quercetin, rutin, resveratrol) or with ascorbic acid; assessment of antioxidant interactions of ascorbic acid – resveratrol, ascorbic acid – ENOXIL mixtures and evaluation of the influence of the concentration, the reaction environment, the order of mixing compounds on the type and mechanisms of antioxidant interaction;
- addressing the study of antioxidant interactions from the perspective of ecovaleology and integration of the results obtained in the Ecological Chemistry course at the Moldova State University for developing students' ecovaleological concepts; formulation and dissemination of conclusions regarding the rational and balanced consumption of antioxidants, and their effective use.

Scientific novelty and originality. For the first time, the type of antioxidant interactions between phenolic compounds and natural organic acids were determined in combinations and concentrations similar to those in grapes. The influence of the reaction conditions on the type of antioxidant interactions has been established. Mechanisms of synergistic action between ascorbic and dihydroxyfumaric acids, and between resveratrol and ascorbic acid have been proposed; mechanisms of antioxidant interaction between phenolic compounds and organic acids in grapes have been suggested. For the first time, the DPPH[•], ABTS^{•+} and PRFe methods were applied to study the antioxidant activity of newly selected autochthonous grape varieties. A new perspective on the topic of antioxidant interactions was offered by addressing the subject from the view of the

ecovaleology concept in order to formulate conclusions regarding the consumption and efficient use of antioxidants.

Research hypothesis. The use or consumption of antioxidants in the combinations and concentrations at which they are found in nature is advantageous and beneficial due to the synergistic, additive or antagonistic effects that occur in multicomponent systems.

Theoretical importance. The obtained results enrich and complement the existing studies, allow the formulation of more accurate ideas regarding the redox mechanisms and processes in which the studied substances may be involved. Also, the investigation's results bring a scientific and didactic contribution regarding the formation of ecovaleological concepts of students from higher education institutions.

The applicative value of the work relies on the possibility of using the results obtained to improve the antioxidant effect and the efficiency of pharmaceutical, cosmetic products and existing technological processes. At the same time, the obtained results can be easily integrated into the curriculum of higher education disciplines.

Implementation of scientific results. The obtained results were integrated into the lecture "Food chemistry and food quality assurance. Antioxidants" which is part of the Ecological Chemistry course elaborated by acad. Gh. Duca at the Moldova State University, and were presented to students during four consecutive years.

Publications on the topic of the thesis. The results on the research topic of the thesis are reflected in 26 scientific works: 3 book chapters published in national and international monographs; 2 articles in international journals with impact factor; 3 articles in national journals; 18 participations in national and international scientific events such as conferences, symposia, summer schools on the topic of ecological chemistry/green chemistry.

THESIS CONTENT

1. MATERIALS AND METHODS USED IN THE STUDY OF ANTIOXIDANT INTERACTIONS

In this chapter, the materials and methods used to achieve the thesis goal and objectives are described. Local grapes of Viorica, Riton, Feteasca Neagă and Copceac varieties were used as raw material; to determine the types of antioxidant interactions, phenolic compounds (catechin, quercetin, rutin, resveratrol, gallic acid) and organic acids (ascorbic, dihydroxyfumaric, tartaric, citric acids) and ENOXIL were used. The following tests of antioxidant activity determination were applied – DPPH[•] (2,2-diphenyl-1-picrylhydrazyl), ABTS^{•+} (2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid)), PRFe (Fe(III) reduction power); several assays to identify classes of natural compounds in grapes were used – Folin-Ciocalteu, DMACA (4-

dimethylaminocinnamaldehyde), differential pH method; also, classic methods of determination of basic physico-chemical parameters of the investigated grape samples were utilised. In terms of laboratory technique, modern physico-chemical analysis methods were used such as UV-Vis (Ultraviolet-Visible) spectroscopy, Stopped-Flow spectroscopy, RES (Electronic Spin Resonance) spectroscopy, NMR (Nuclear Magnetic Resonance) spectroscopy, capillary electrophoresis.

In order to integrate the concept of ecovaleology into the lecture of the Ecological Chemistry course, expository oral communication methods (lecture, explanation, logical demonstration) and conversational (free discussion, problematization), mediated exploration methods (analysis of experimental results, analysis comparative), methods based on real action (case study analysis) were used.

2. CHARACTERIZATION OF THE CHEMICAL COMPOSITION OF LOCAL GRAPES AT DIFFERENT MATURATION PERIODS

2.1. Basic and specific physico-chemical indices of local grapes

Physico-chemical parameters are the first indicators of the quality of grapes and their degree of maturation. From Table 2.1, the physico-chemical indicators vary depending on the degree of maturation of the grapes [5].

Table 2.1. Basic physico-chemical indices determined of Riton, Viorica, Feteasca Neagră and Copceac grape varieties at different stages of ripening. Analyses were performed in pressed grape juice.

Degree of maturity	Variety name	Sugar content, g/L	Titrateable acidity, g-ech. H ₂ SO ₄ /L	pH	Redox potential, mV
Unripen grapes	Riton	35.74±7.21	30.01±7.39	2.36±0.14	245.57±17.91
	Viorica	33.11±3.54	29.06±10.79	2.28±0.61	264.90±2.14
	Feteasca N.	43.39±10.89	25.27±2.58	2.37±0.15	260.17±7.94
	Copceac	39.78±8.65	28.01±6.19	2.43±0.10	254.83±7.01
Grapes at veraison	Riton	140.25±10.82	9.15±2.19	2.61±0.16	245.55±8.98
	Viorica	158.13±14.42	9.73±1.68	2.79±0.13	235.35±8.13
	Feteasca N.	116.33±23.05	10.74±1.83	2.63±0.11	245.05±6.01
	Copceac	130.05±39.67	8.61±4.38	2.66±0.13	243.25±7.57
Ripe grapes	Riton	215.73±16.59	5.17±0.06	2.82±0.09	233.85±6.15
	Viorica	221.85±32.46	5.79±0.55	2.91±0.02	228.70±1.27
	Feteasca N.	241.23±23.81	4.41±0.83	2.91±0.51	228.45±29.49
	Copceac	229.52±21.64	5.03±1.16	2.95±0.53	226.61±31.11

The sugar content increases from 38 g/L (average) in unripen grapes to about 136 g/L at the veraison, and reaches an average of 227 g/L in ripe grapes – this sugar content is considered optimal for harvest and wine production. The evolution of titrateable acidity is inversely proportional to the content of sugars. Thus, this index decreases from approximately 28 g-ech. H₂SO₄/L in unripe grapes up to about 5 g-ech. H₂SO₄/L in ripe berries [5]. The pH determined in

the analysed samples increases from approximately 2.4 in unripe grapes to an average of 2.9 in ripe ones [5]. This increase in pH values is determined by the decrease in titratable acidity. Being inversely proportional to pH, the redox potential drops from an average of 256 mV in unripe grapes to about 228 mV in ripe berries.

According to Figure 2.1, tartaric and malic acids represent approximately 90% of the total organic acids in grapes; citric and oxalic acids are also present at lower concentrations.

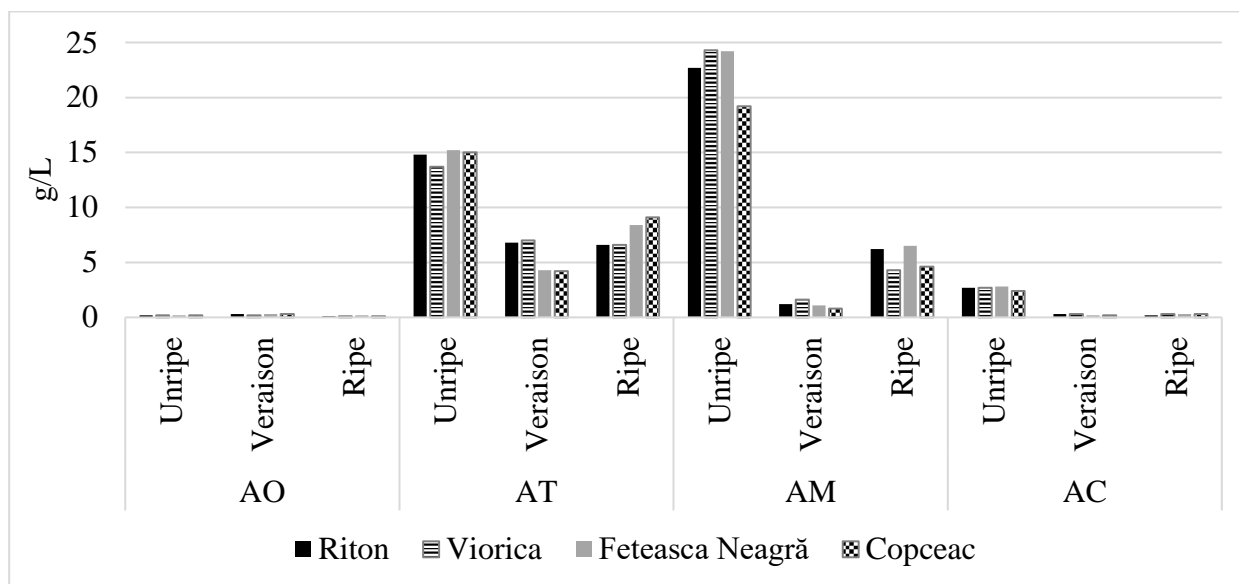


Figure 2.1. The content of organic acids - oxalic (AO), tartaric (AT), malic (AM), citric (AC), determined in unripe, at veraison and ripe grapes of Riton, Viorica, Feteasca Neagră and Copceac varieties

Tartaric and malic acids reach maximum values of about 15 g/L and 22 g/L, respectively, in unripe berries [6, 7]. These peak values are followed by a sharp decrease during the veraison period, down to 6 – 8 g/L for AT and 1 – 2 g/L for AM. At ripening, AT and AM content increase to an average of 8 g/L and 5 g/L, respectively. Organic acids AO and AC are found in grapes, especially in ripe ones, in a small amount that does not exceed 1 g/L, except for AC in green grapes, which register values of about 3 g/L (Figure 2.1) [6, 7].

Total content of phenolic compounds, proanthocyanidins and anthocyanins in local grapes.

Figure 2.2 shows that unripe grapes have the highest content of phenolic compounds, about 4 g-equivalent AG per liter (g EAG/L) [7–9]. The concentration of phenolic compounds decreases significantly in the Viorica, Riton and Feteasca Neagră varieties during veraison and ripening periods. Thus, in ripe grapes the total content of phenolic compounds reaches 1.2 – 1.5 g EAG/L in white varieties and 2.4 g EAG/L in Feteasca Neagra grapes [7–9]. In the case of the Copceac variety, the total content of phenolic compounds registers a moderate decrease to 3.1 g EAG/L at veraison, this value being maintained until ripening [7–9].

The decrease in the content of phenolic compounds is due to the migration of polyphenols from the pulp to the seeds and skin. According to Figure 2.3, the highest content of proanthocyanidins is recorded in unripe grapes, especially in Viorica variety – approximately 1.2 g-equivalent Cat per liter (g ECat/L) [7–9]. During maturation, the given index decreases to an average of 0.43 g ECat/L in ripe Riton, Viorica and Copceac berries, and to 0.24 g ECat/L in Feteasca Neagră variety [7–9].

The formation of red pigments in Feteasca Neagră and Copceac grapes during the veraison and ripening periods is demonstrated in Figure 2.4. The maximum content of anthocyanins is observed for the Copceac grape variety, which contains approximately 500 mg-equivalents of Malvidin per liter (mg EMalv/L) at the veraison and 875 mg EMalv/L in ripe grapes [7–9]. Lower concentrations of anthocyanins are determined in Feteasca Neagră variety, namely 300 mg EMalv/L at the veraison and approximately 700 mg EMalv/L in ripe berries [7–9]. Anthocyanin compounds are formed in red grapes varieties starting from veraison period, their content being doubled at the ripening [7–9].

Phenolic compounds, including proanthocyanidins and anthocyanins, can reduce free radicals in natural systems, therefore their content influences the antioxidant activity of grapes.

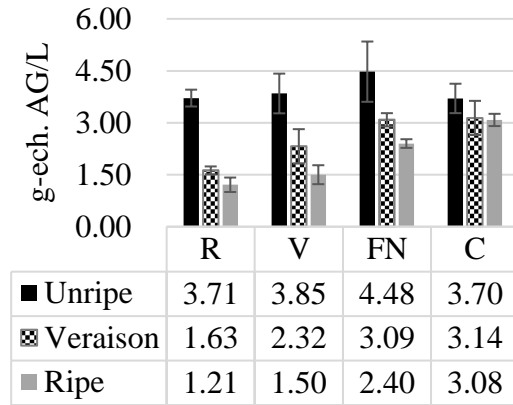


Figure 2.2. The total content of phenolic compounds determined for unripe, at veraison and ripe grapes of Riton (R), Viorica (V), Feteasca Neagră (FN) and Copceac (C) varieties

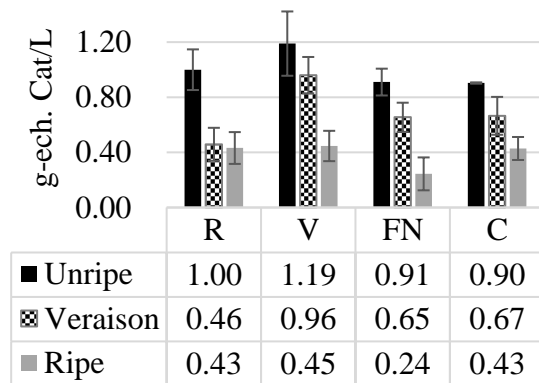


Figure 2.3. The proanthocyanidins content determined in unripe, at veraison and ripe grapes of Riton (R), Viorica (V), Feteasca Neagră (FN) and Copceac (C) varieties

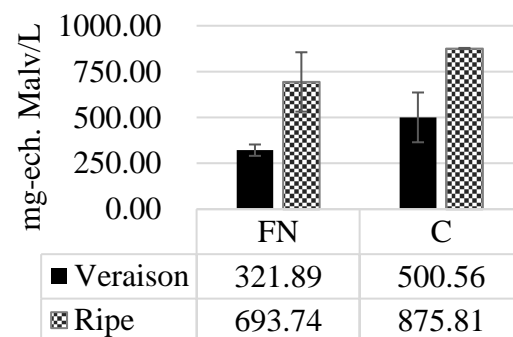


Figure 2.4. The anthocyanins content determined in unripe and ripe grapes of Feteasca Neagră (FN) and Copceac (C) varieties

2.2. The antioxidant activity of studied grape varieties

The antioxidant activity of local grape varieties has been determined by using three methods described in the specialized literature – DPPH[•], ABTS^{•+} and PRFe. According to Figure 2.5, the highest antioxidant activity in the reaction with DPPH[•] is observed for unripe grapes and exceeds 2 g AA-equivalents per liter (g EAA/L) [8–10]. The extracts from grapes at veraison and ripe ones have a lower antioxidant activity, especially in the case of Riton and Viorica white grape varieties – approximately 0.6 g EAA/L; the Feteasca Neagră and Copceac grapes demonstrate an antioxidant activity equivalent to approximately 1.6 g EAA/L [8–10]. This fact is caused by the formation and accumulation of anthocyanins during the veraison and ripening period, which are compounds that effectively annihilate DPPH[•].

Results on the antioxidant activity determined by the ABTS^{•+} method are expressed in Trolox equivalents (g ETrolox/L) (Figure 2.6). Thus, unripe grape extracts possess the highest antioxidant activity of approximately 8 g ETrolox/L [8–10]. In the ripe grapes of Riton and Viorica, the antioxidant activity decreases to 1.6 g ETrolox/L, and in the case of the Feteasca Neagră and Copceac varieties - to an average of 5 g ETrolox/L. Similarly, this difference between the white and red varieties is due to the presence of anthocyanins in red grapes [8–10].

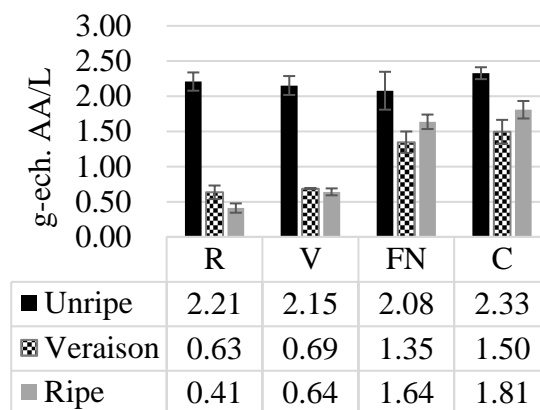


Figure 2.5. Antioxidant activity of unripe, at veraison and ripe grapes of Riton (R), Viorica (V), Feteasca Neagră (FN) and Copceac (C) varieties determined by DPPH[•] method

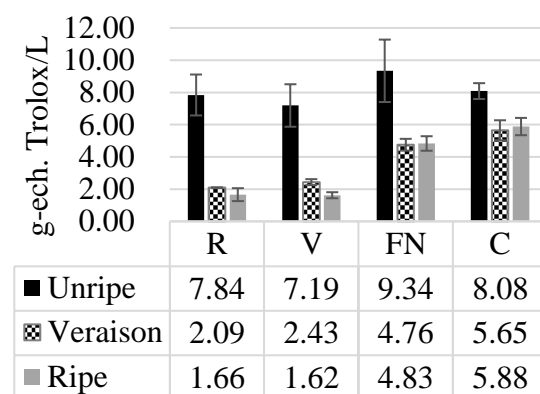


Figure 2.6. The antioxidant activity of unripe, at veraison and ripe grapes of Riton (R), Viorica (V), Feteasca Neagră (FN) and Copceac (C) varieties determined by ABTS^{•+} method

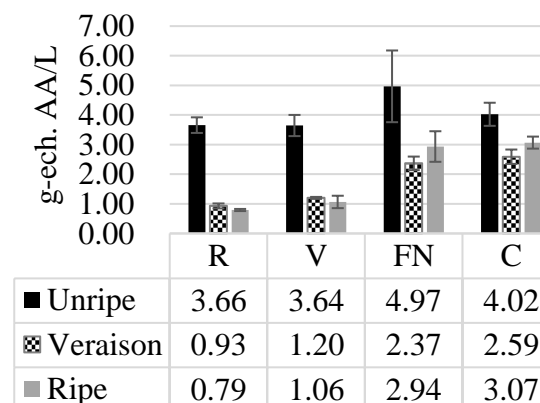


Figure 2.7. Antioxidant activity of unripe, at veraison and ripe grapes of Riton (R), Viorica (V), Feteasca Neagră (FN) and Copceac (C) varieties determined by PRFe method

Extracts obtained from unripe grapes demonstrate the highest Fe(III) reduction power – greater than 3.6 g EAA/L (Figure 2.7), which is also considered the highest prooxidant activity [8–10]. Along with the decrease of the content of phenolic compounds (Figure 2.2) and the content of proanthocyanidins (Figure 2.3), the Fe(III) reduction power of grapes' extracts is also decreasing in white grapes during the veraison and ripening, being noticed values of approximately 1 g EAA/L [8–10]. On the other hand, for the Copceac and Feteasca Neagră red varieties, the PRFe indicator exceeds the value of 2.4 g EAA/L during the same periods, due to the accumulation of high concentration of anthocyanins.

2.3. Establishment of the optimal concentrations of phenolic compounds and organic acids for the study of antioxidant interactions

The experimental results described in this chapter, as well as the data known in the specialized literature, allowed the establishment of the optimal concentrations and ratios for carrying out the experiments to determine the antioxidant interactions between the studied compounds (Table 2.2

Table 2.2. Concentration ratios of phenolic compounds and organic acids in grapes according to data reported in the literature and experimental data. Concentration ratios used in experiments to determine antioxidant interactions

Concentration ratios								
		According to the data from the specialized literature		According to experimental data		Concentration ratios used for IA determination		
Organic acid		AT	AC	AT	AC	AT	AC	DHF
Antioxidant compound	AA	11- 173	1 - 9	31 - 154	5 - 25	1 - 700	1 - 700	0.1 - 5
	AG	11 - 10113	0.2 - 706	11456	1901	1 - 2500	1 - 1500	0.1 - 5
	Cat	3 - 6578	0.1 - 459	7452	1237	1 - 1000	1 - 1000	0.1 - 5
	Que	8 - 21856	0.1 - 1116	1490	247	1 - 800	1 - 800	0.1 - 10
	Rut	10 - 3686	0.2 - 297	437	73	1 - 900	1 - 900	0.1 - 10
	Res	114 - 29706	1.6 - 2392	1694	281	1 - 5000	1 - 4000	0.05 - 5

Table 2.2 contains the concentration ratios between the highest and lowest concentrations of compounds identified in grapes according to the specialized literature and data obtained experimentally in local grape varieties, and the range of concentration ratios at which the antioxidant and non-antioxidant compounds were combined to establish the type of IA.

Thus, in mixtures with tartaric or citric organic acids, the concentration ratios studied vary for each compound – ascorbic acid: 1 – 700, gallic acid: 1 – 2500, catechin: 1 – 1000, quercetin: 1 – 800, rutin: 1 – 900 and resveratrol: 1 – 5000; and in mixtures with dihydroxyfumaric acid, the ratios are in the range of 0.05 – 10

3. ANTIOXIDANT INTERACTIONS BETWEEN NATURAL COMPOUNDS FROM GRAPES

According to specialized literature, antioxidant interactions can be synergistic, additive and antagonistic depending on the concentration and combination of compounds [11]. The explanations regarding the IA mechanism between the given compounds refer to (1) regeneration processes, (2) the formation of intermolecular complexes, dimers or antioxidant adducts and (3) complementary effects involving the effect of solvent, pH, concentration, solubility, etc. [11]. At the same time, the presence of polymerization processes between phenolic compounds leads to a decrease in the number of electron-donating groups and to the manifestation of antagonistic effects [11]. Organic acids such as tartaric and citric acids are non-antioxidant compounds that are found in large quantities in grapes and can influence the antioxidant activity of reducing compounds [12]. The same studies proved the presence of synergistic effects between various free radical scavengers and organic acids in grapes.

3.1. Antioxidant interactions between grape phenolic compounds and organic acids

Antioxidant interactions between catechin and organic acids. The phenolic compound Cat, in the presence of organic acids, demonstrates a progressive evolution of IA values – from strong antagonistic effects to additive effects (Figure 3.1, cases A and F) [13]. Both, in combination with AT and AC, antagonistic effects were observed at low concentrations of Cat (0.33 – 0.93); once the concentration of Cat was increased, additive antioxidant interactions have been noticed [13]. Changing the AT or AC content did not significantly affect the antioxidant activity of Cat. The presence of acid ions in the reaction mixture inhibits the deprotonation of phenolic compound and thereby the SPLET (sequential proton loss electron transfer) mechanism of action, so the electron donor is the parent molecule.

Antioxidant interactions between gallic acid and organic acids. In the mixtures of AG and AT or AC (Figure 3.1, cases B and G), mostly additive effects (0.96 – 1.04) and antagonistic effects (0.64 – 0.92) have been observed [13]. In the presence of AT, IA values (Figure 3.1) are lower at low AG concentrations, but increase to additive interactions once AG/DPPH[•] molar ratios become higher [13]. The only moderate synergistic effect of 1.05 was recorded for the AG – AT interaction at the AG/DPPH[•] molar ratio of 0.20 and the AT concentration of 16×10^{-4} N [13].

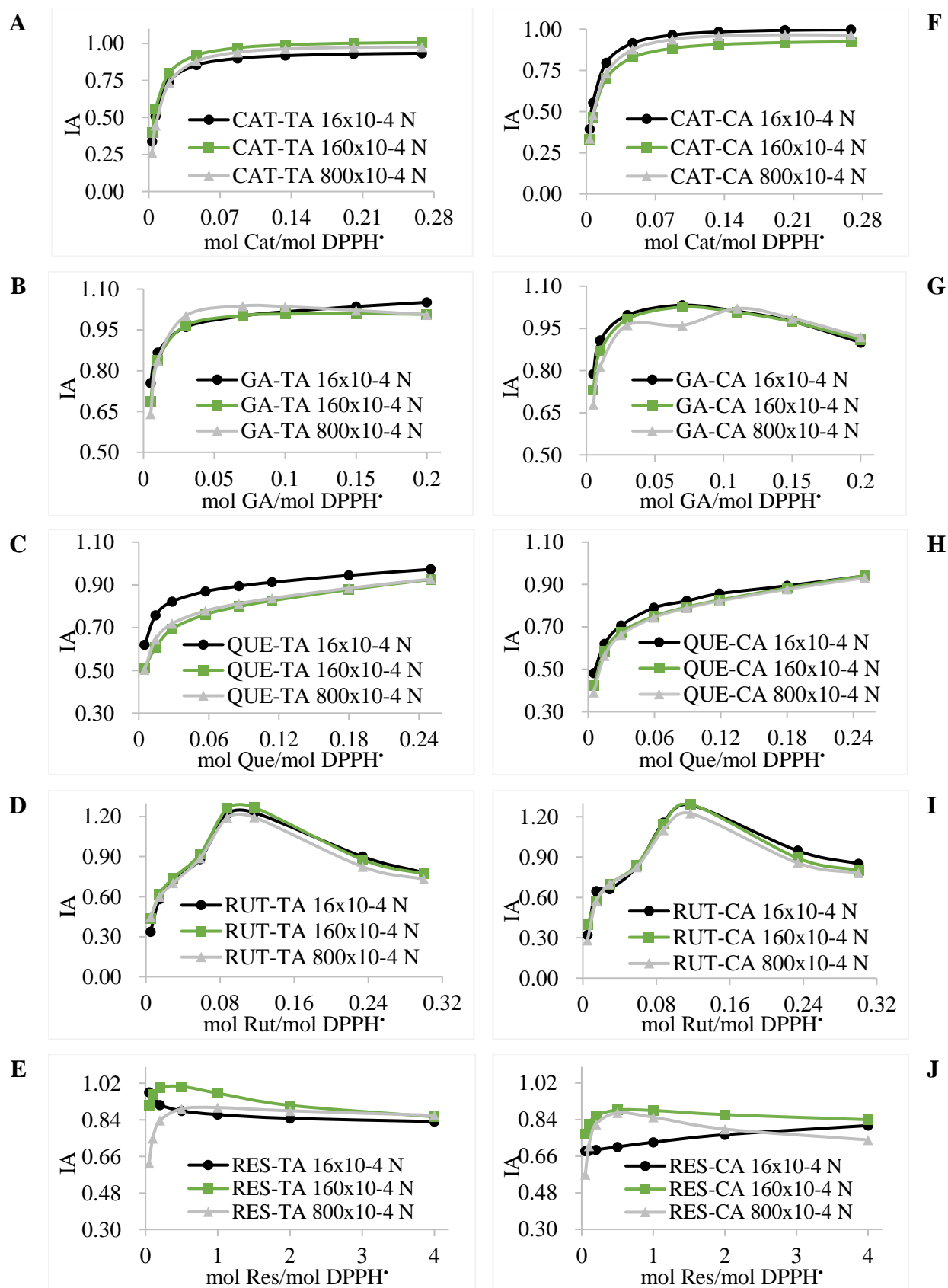


Figure 3.1. Antioxidant interactions (IA) between phenolic compounds (Cat, AG, Que, Rut, Res) in combination with different concentrations of AT (A, B, C, D, E) or AC (F, G, H, I, J) [13]

In combination with AC, the mixture of compounds showed an upward trend followed by a downward one in terms of IA. AG – AC mixtures did not show synergistic effects, but only additive and antagonistic interactions [13].

Antioxidant interactions between quercetin and organic acids. The antioxidant interactions between different concentrations of Que and AT or AC have been found to be only antagonistic (in the range 0.50 – 0.94 and 0.39 – 0.94, respectively), except for an additive interaction (0.97) observed for the Que – AT mixture (Figure 3.1, cases C and H) [13]. Figure 3.1C, demonstrates that higher concentrations of AT negatively influence the antioxidant activity of the phenolic compound [13]. The given fact and the persistence of the antagonistic effects independent of AT or AC concentration underline the idea that in acidic environments the antiradical activity of polyphenols diminishes. Similar to catechin, the Que molecule is more stable at low pH and therefore less susceptible to oxidation.

Antioxidant interactions between rutin and organic acids. Although structurally Que and Rut have similar flavonoid moiety, Rut exhibits different behaviour in the presence of organic acids. At the lowest polyphenol concentrations, strong antagonistic effects were observed, in the range 0.29 – 0.92 (Figure 3.1, cases D and I) [13]. However, at Rut/DPPH^{*} ratios of 0.09 and 0.12, significant synergistic interactions of 1.19 and 1.27 (for the Rut – AT mixture) and 1.10 and 1.29 (for the Rut – AC mixture) have been recorded [13]. The synergistic effect decreases with the increase of Rut content. At the same time, the obtained results indicate that the antioxidant interactions between Rut and AT or AC are hardly dependent on the concentration of organic acids [13]. These results indicate that, in the case of Rut – AT or Rut – AC combinations, the synergistic effect is mainly based on the polyphenol concentration and the presence of organic acids in the reaction mixture, since the antioxidant activity of Rut in the absence of AT or AC is lower for the Rut/DPPH^{*} molar ratios of 0.09 and 0.12 [13].

Antioxidant interactions between resveratrol and organic acids. Res stilbene showed mostly antagonistic effects in the presence of organic acids (Figure 3.1, cases E and J) [13]. The strongest antagonistic interactions have been determined for the concentration of AT or AC of 16×10^{-4} N, but for the concentration of 160×10^{-4} N the weakest antagonistic effect has been recorded [13]. Similar to catechin and quercetin, in acidic media Res ionization is suppressed, together with the SPLET mechanism of action, therefore the antioxidant activity is lower.

Figure 3.2 is a generalized representation of the effect that organic acids have on the antioxidant activity of phenolic compounds [13]. Phenolic compounds are effective antioxidants through the SPLET mechanism, which occurs once the parent molecule ionizes.

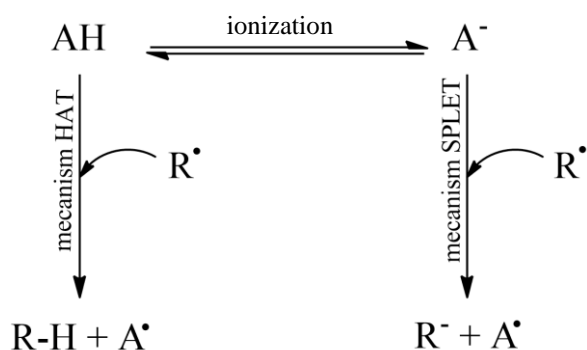


Figure 3.2. Illustration of the dependence of action mechanism of antioxidant in presence of organic acids AT or AC and the ionization of the molecule [11]

In the presence of organic acids, ionization is suppressed and the HAT (hydrogen atom transfer) mechanism becomes operative, therefore the antioxidant activity decreases, since phenolic compounds are not so efficient in annihilating radical species through the HAT mechanism. The exception to this scheme is the compound Rut, which at certain concentrations exhibits a strong synergistic effect due to polymerization process

3.2. Antioxidant interactions between grape phenolic compounds and dihydroxyfumaric acid

Antioxidant interactions between catechin and dihydroxyfumaric acid. According to Figure 3.3A, the antioxidant interactions between Cat and DHF are found to be dependent on the organic acid concentration [13]. The maximum values of synergistic interactions, of approximately 1.08, have been observed in all samples with the lowest concentration of DHF (2×10^{-4} N) [13]. Increasing the DHF content causes significant changes in total antioxidant activity and IA values; thus, the antioxidant activity decreases in samples with 4×10^{-4} N and 8×10^{-4} N of DHF, observing mostly additive interactions [13].

Antioxidant interactions between gallic acid and dihydroxyfumaric acid. AG – DHF mixtures possess, mainly, antagonistic effects in the range 0.43 - 0.82. From Figure 3.3B it can be seen that increasing the concentrations of both compounds improves the total antioxidant activity of the mixtures, however, most of the interactions remain within the range of antagonistic IA values [13]. The samples formed by AG/DPPH[•] in a molar ratio of 0.12 in combination with DHF demonstrated the highest value of IA (maximum of 0.90), followed by a moderate decrease in IA values [13].

Antioxidant interactions between quercetin and dihydroxyfumaric acid. Mixtures of Que and DHF showed mainly additive effects that did not exceed the value of 0.99 [13]. According to Figure 3.3C, a higher concentration of DHF negatively influences the total antioxidant activity of the solutions and intensifies the antagonistic effects, especially in mixtures with lower concentrations of Que [13].

Antioxidant interactions between rutin and dihydroxyfumaric acid. Multiple moderate synergistic interactions, in the range of 1.05 – 1.08, were observed for Rut – DHF mixtures (Figure 3.3D) [13]. Different concentrations of DHF produce different effects and trends in terms of IA values [13]. For example, Rut in combination with 2×10^{-4} N DHF shows synergistic effects of 1.05 regardless of the change in Rut content [13]. For the second DHF concentration of 4×10^{-4} N, the IA values start with 0.96 and increase up to 1.07 as the Rut/DPPH* molar ratio increases [13]. At the concentration of 8×10^{-4} N DHF, the highest synergistic effect of 1.07 was observed for the Rut/DPPH* ratio of 0.11, followed by a significant decrease in IA values [13].

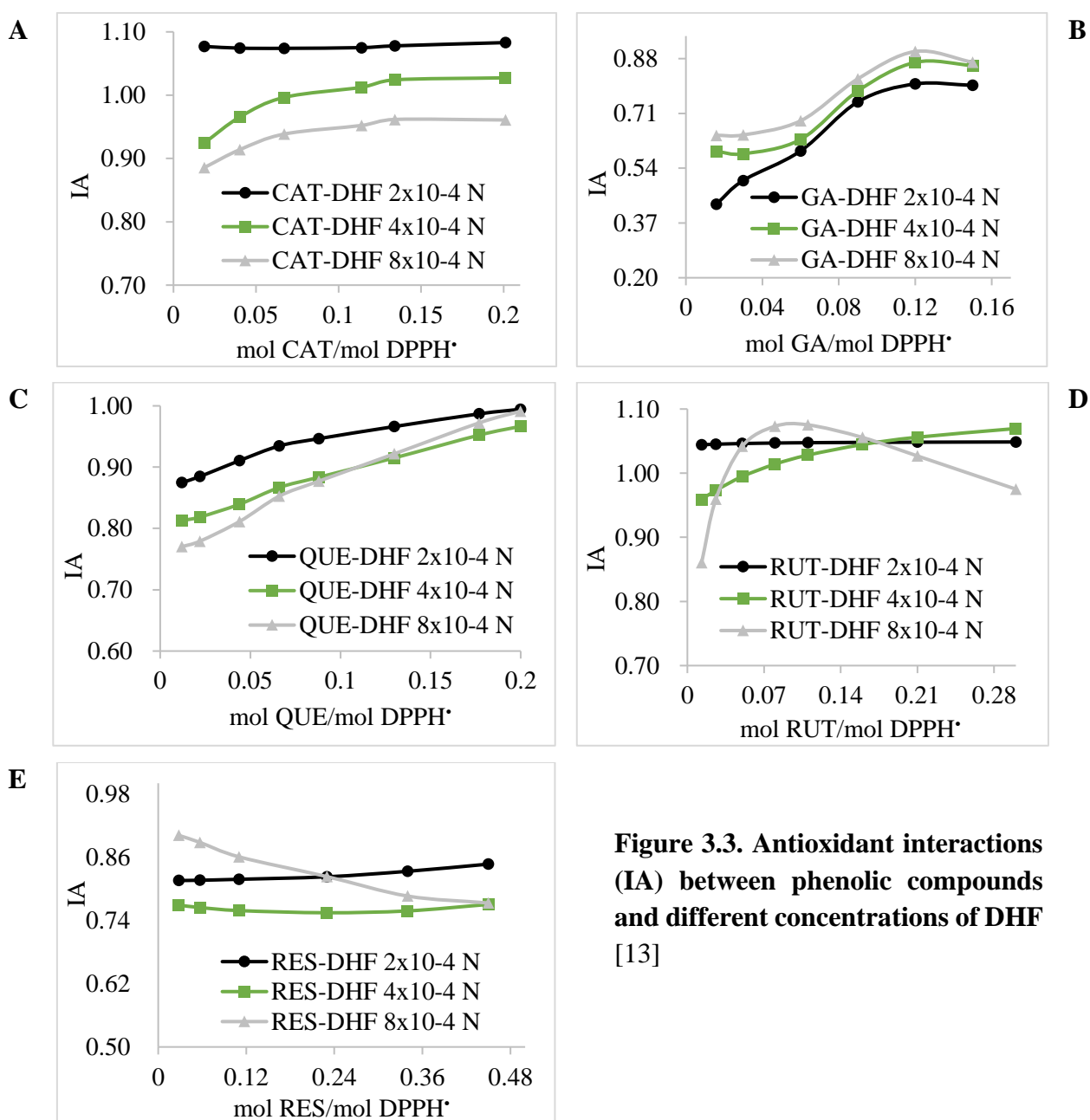


Figure 3.3. Antioxidant interactions (IA) between phenolic compounds and different concentrations of DHF [13]

Antioxidant interactions between resveratrol and dihydroxyfumaric acid. Mixtures of Res and DHF demonstrated mostly antagonistic effects (0.75 – 0.83) and only some additive

interactions (0.85 – 0.90) (Figure 3.3E) [13]. The data on the mixtures formed by Res and the first two concentrations of DHF – 2×10^{-4} N and 4×10^{-4} N, demonstrate that the IA values decrease significantly with the increase of the DHF concentration [13]. In mixtures with 8×10^{-4} N DHF, IA evolves negatively – from additive to antagonistic effects, once the Res content increases [13].

3.3. Antioxidant interactions between ascorbic acid and other grape compounds

Antioxidant interactions between ascorbic acid and tartaric and citric acids. Figure 3.4 shows that AT has a better influence than AC on the antioxidant activity of AA, being noticed six combinations of AA – AT with synergistic effect, and only one combination of AA – AC with the same effect [13]. In both cases, the samples with lower concentrations of AT or AC – 16×10^{-4} N and 160×10^{-4} N, demonstrated better antioxidant activity, registering synergistic effects of maximum 1.08 for the AA – AT mixture and 1.06 for AA – AC [13].

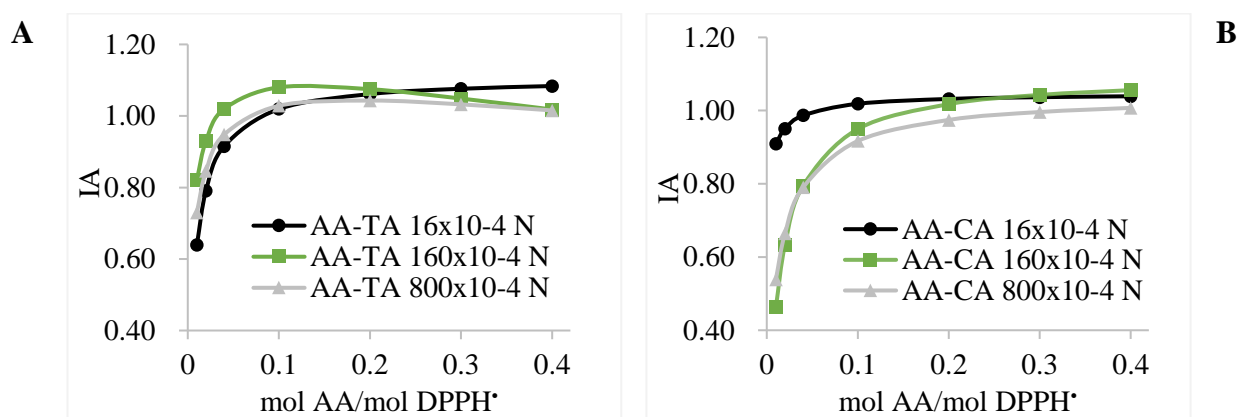


Figure 3.4. Antioxidant interactions (IA) between ascorbic acid (AA) and A) tartaric (AT) and B) citric (AC) acids [13]

The enhancement of the antioxidant activity of AA in the presence of organic acids may be due to the mechanism of action of this free radical scavenger. In this reaction medium, AA ionization is suppressed due to the high concentration of AT or AC ions present in the solution (Figure 3.5). Consequently, the SPLET mechanism is inhibited and the HAT mechanism becomes operative for the annihilation of DPPH^\bullet . Compound AA acts efficiently through the HAT mechanism by donating two H atoms to radical species.

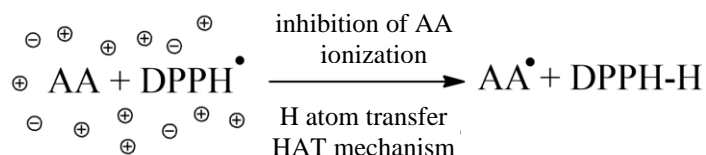


Figure 3.5. HAT mechanism of DPPH^\bullet annihilation by AA in the presence of organic acids AT or AC

Antioxidant interactions between ascorbic acid and dihydroxyfumaric acid. The results obtained by Stopped-Flow spectroscopy in 98% ethanol (EtOH) and in the wine matrix

demonstrated that in wine matrix the antioxidant activity of the individually tested compounds in the reaction with DPPH[•] is significantly higher. According to Table 3.1, where the observed rate constants (k_{obs}) for AA and DHF compounds, used in different concentrations, are represented, it can be observed that the k_{obs} values for DHF are 10 times higher in the wine matrix compared to those in 98% ethanol, and k_{obs} for AA are twice as high in the wine matrix [14].

Table 3.1. Observed rate constants determined in 98% ethanol and wine matrix for DHF and AA reacting with DPPH[•] [14]

Sample	Concentration, mM	$k_{\text{obs}}, \text{S}^{-1}$	
		98% Ethanol	Wine matrix
DHF	0.06	0.368 ± 0.049	3.656 ± 0.496
	0.12	0.350 ± 0.030	3.863 ± 0.155
	0.18	0.383 ± 0.054	3.371 ± 0.091
	0.40	0.167 ± 0.024	2.277 ± 0.049
	0.60	0.107 ± 0.076	2.122 ± 0.032
	0.80	0.040 ± 0.016	2.181 ± 0.057
AA	0.06	0.328 ± 0.036	0.654 ± 0.021
	0.12	0.327 ± 0.017	0.653 ± 0.006
	0.18	0.385 ± 0.020	0.681 ± 0.015

Results regarding the antioxidant capacity of AA – DHF combinations reveal the same trend as in the case of using a single antioxidant in reaction with DPPH[•]. In 98% ethanol all mixtures show low antioxidant activity compared to values obtained in the wine matrix (Figure 3.6) [14].

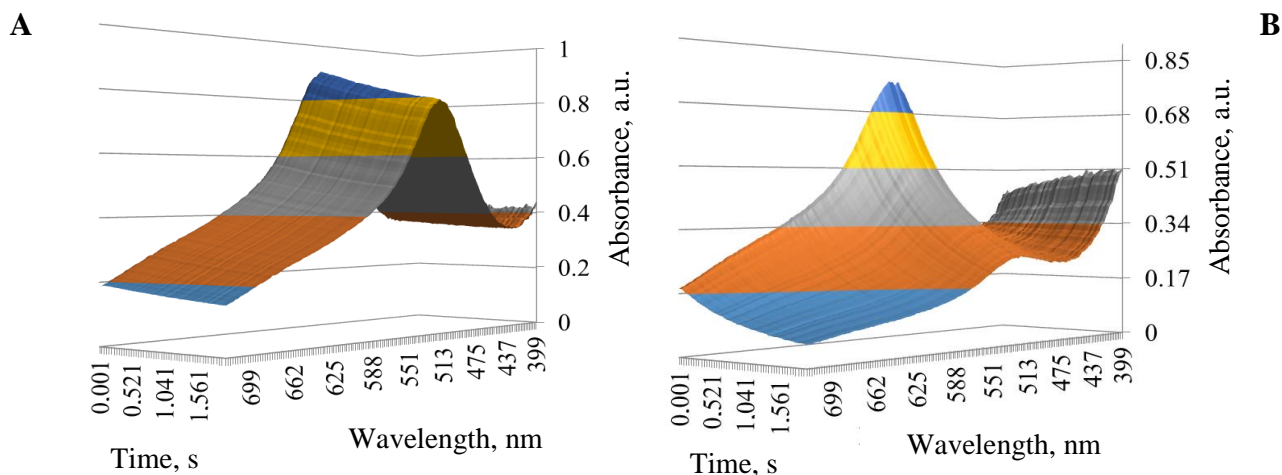


Figure 3.6. Decrease in absorbance after the interaction of DPPH[•] with the mixture of DHF (0.18 mM) – AA (0.18 mM) in (A) 98% EtOH and (D) wine matrix [14]

Figure 3.6 demonstrates the effect of the solvent on the reaction kinetics and the free radical reduction capacity of the studied acids [14]. In both examples shown in Figure 3.6, the same concentration of antioxidants was used – 0.18 mM, however in the wine matrix DPPH[•] is almost completely annihilated after 2 seconds [14]. For mixtures with the highest antioxidants'

concentration, the greatest efficiency in ethanol is 20%, while in the wine matrix the same combination of antioxidants captures 85% of DPPH[•] [14].

The Stopped-Flow spectroscopy allowed to obtain results regarding the kinetics of the redox interaction for the first 2 seconds of the reaction. This time proved to be insufficient for the reaction to reach the steady state, therefore UV-Vis spectroscopy investigations were carried out. The IA values between AA – DHF determined by the UV-Vis method evolve from antagonistic to synergistic effects as a consequence of the concentration increase of both antioxidants (Figure 3.7).

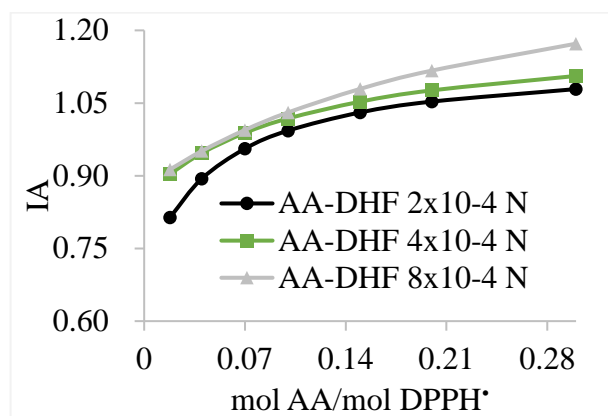


Figure 3.7. Antioxidant interactions between ascorbic and dihydroxyfumaric acids

Therefore, the highest value characterizing a synergistic interaction – 1.17, was obtained for the AA/DPPH[•] molar ratio of 0.30 in combination with 8×10^{-4} N of DHF (Figure 3.7), which represents the highest concentrations of AA and DHF used in this experiment [13].

To determine the types of antioxidant interaction between AA and DHF by RES spectroscopy, several concentration ratios of mM DHF/mM AA: 0.5, 0.6, 0.7, 1, 1.4, 1.7 and 2, have been used in the reaction with DPPH[•], as is illustrated in Figure 3.8 [15, 16]. Among the 7 ratios investigated, the ratio mM DHF/mM AA = 1 gave the weakest result of 0.93, being characteristic for additive interactions [15]. The mM DHF/mM AA ratios of 1.4 and 1.7 demonstrated the strongest synergistic effect of 1.24 and the highest antioxidant activity [15]. This fact is also observed from the analysis of the theoretically calculated and experimental DPPH[•] inhibition percentages (Figure 3.8) [15, 16]. Finding the ratio mM DHF/mM AA = 1.7 to be the one that possesses the strongest synergistic effect and efficiently inhibits DPPH[•], the dependence of the synergistic effect on the total concentration of antioxidants was further investigated, respecting in all samples the ratio mM DHF/mM AA = 1.7 (Figure 3.9) [15, 16]. This fact allowed the determination of the FIC index, which is another method of calculating the type of antioxidant interaction between compounds. Thus, the FIC index for the ratio mM DHF/mM AA = 1.7 was established as 0.9, a value that describes a synergistic interaction between the two antioxidants [15, 16].

Using NMR spectroscopy, the synergistic interaction mechanism between AA and DHF was studied in methanol-*d*₄/acetone-*d*₆ and methanol-*d*₄/chloroform-*d*₁ solvents mixtures (Figure 3.10). The mutual regeneration of the antioxidants AA and DHF was shown to be dependent on the nature of the solvents used, in the present case, the given hypothesis being valid only in the medium of

methanol- d_4 /chloroform- d_1 , where the partial regeneration of ADA by DHF was established [17, 18] (Figure 3.10B).

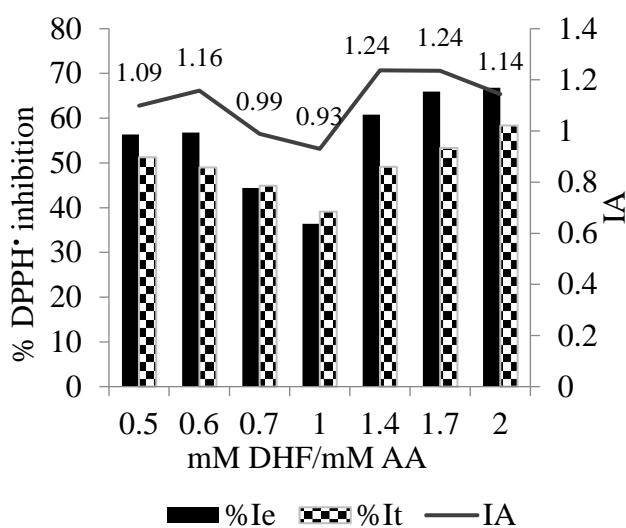


Figure 3.8. Representation of %DPPH[•] Inhibition experimentally determined (%Ie) and theoretically calculated (%It) (left axis); representation of the type of antioxidant interaction for each mM DHF/mM AA ratio (right axis) [15, 16]

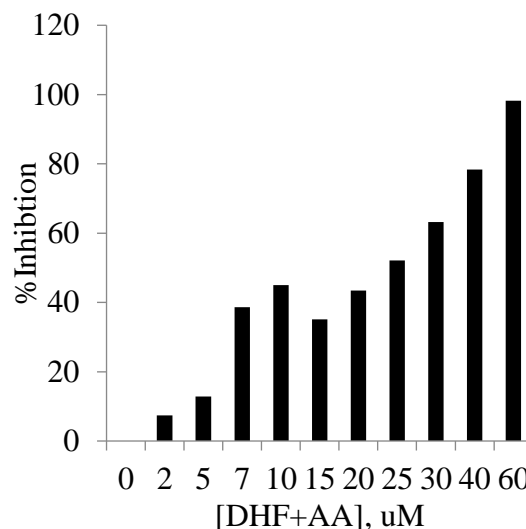


Figure 3.9. Illustration of the dependence of the DPPH[•] inhibition percentage on the total concentration of antioxidants (DHF+AA, μ M) combined in the ratio mM DHF/mM AA = 1.7; [15, 16]

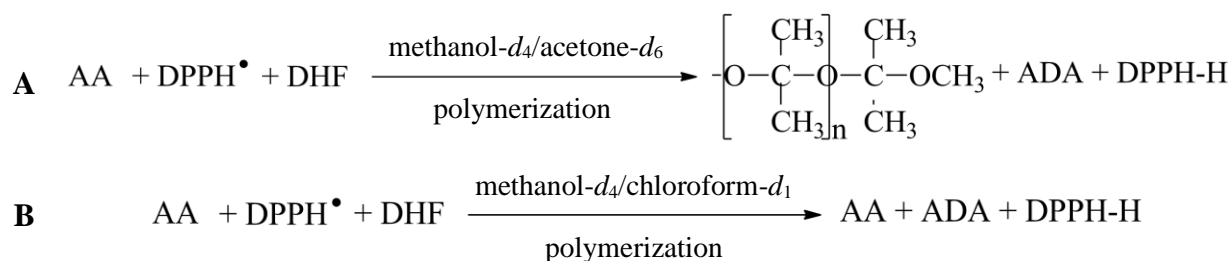


Figure 3.10. General schemes of antioxidant action mechanisms of AA – DHF mixtures in methanol- d_4 /acetone- d_6 (A) and methanol- d_4 /chloroform- d_1 (B)

This mechanism of action is directly related to the polymerization or decarboxylation processes that, due to NMR spectroscopy, were noticed in solution and that depend on the solvents used (Figure 3.10). Therefore, it can be assumed that similar regeneration processes between antioxidants may occur in 96% EtOH.

Although it cannot be stated with certainty what is the mechanism of antioxidant interaction operative in the AA – DHF combination, it has been established that 1) partial regeneration processes between AA and DHF occur under certain reaction conditions and that 2) DHF is the compound that regenerates AA. Also, the solutions consisting of 96% EtOH, AA and DHF possess

relatively high acidity – 3.64 to 4.04, characterized by the predominance of the *keto*- form, which may cause partial decarboxylation of DHF.

Antioxidant interactions between ascorbic acid and resveratrol. In the current UV-Vis spectroscopy investigation, three experimental approaches were followed, with the aim of understanding the effect on the antioxidant activity of the order of adding compounds to the reaction: I) mixing the antioxidants in a 1:1 Res/AA molar ratio, followed by the addition of DPPH[•] (reaction time – 1 hour); II) mixing Res and DPPH[•] (reaction time - 1 hour), then adding AA (reaction time – 15 min); III) mixing AA and DPPH[•] (reaction time – 15 min), then adding Res (reaction time – 1 hour) [19–21]. From Figure 3.11, it can be seen that only approach II, which involves the interaction of Res with DPPH[•], followed by the addition of AA, provides a pronounced synergistic effect of 1.19 [19–21]. The results represented in Figure 3.11 demonstrate that, under these reaction conditions, (1) both synergistic and antagonistic IA are possible between the same concentrations of Res and AA, also (2) the consecutiveness of the addition of compounds in the reaction is a determining factor for the manifestation to a certain type of IA among antioxidants [19–21].

To investigate the impact of compounds' concentration on the antioxidant activity, different molar ratios of Res/AA were tested in the reaction with DPPH[•], following the second approach of carrying out the experiment (Figure 3.12).

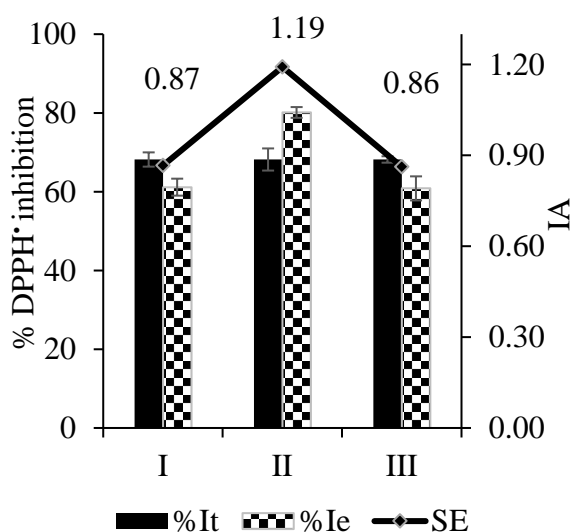


Figure 3.11. Plot of Inhibition experimentally determined (%Ie) and theoretically calculated (%It) (left axis), and IA for approaches I, II and III (right axis) [19–21]

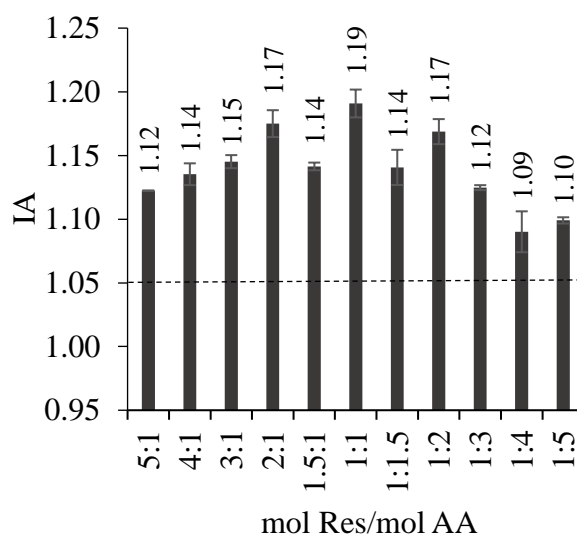


Figure 3/12. Graphical representation of antioxidant interactions of different Res/AA molar ratios. Values greater than 1.05 (above the dashed line), inclusive, are characteristic of synergistic IA [19–21]

Figure 3.12 demonstrates that all samples with different Res/AA molar ratios, from 5:1 to 1:5, possess synergistic effect [19–21]. The strongest synergistic effect – 1.19, was recorded for the 1:1 Res/AA molar ratio, followed by 2:1 and 1:2 Res/AA ratios with synergistic effects of 1.17 each [19–21]. Molar ratios of 1.5:1 and 1:1.5 Res/AA recorded an IA value of 1.14. As the concentration difference between the two antioxidants becomes larger, the synergistic effects decrease (Figure 3.12) [19–21]. The lowest IA value of 1.09 was observed for the 1:4 Res/AA molar ratio [19–21].

According to data obtained by NMR spectroscopy, the synergistic effect between AA and Res is due to the formation of *trans*- δ -viniferins. The approach followed is important for the formation of these compounds (Figure 3.13). When Res and DPPH^{*} initially interact, then AA is added, the manifestation of the synergistic effect can be noticed. Therefore, the Res – AA combination follows the mechanism of “formation of intermolecular complexes, dimers or adducts” to generate synergistic effect [19–21].

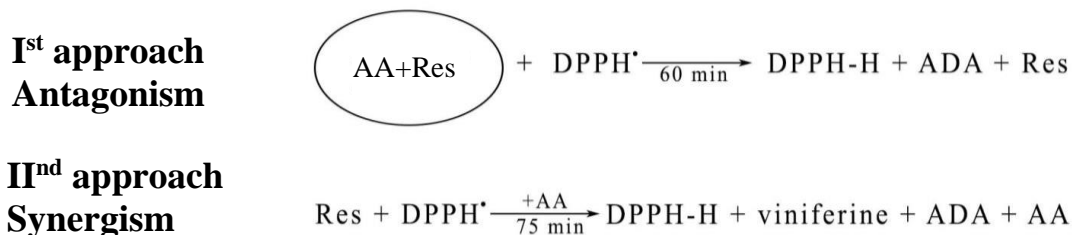


Figure 3.13. Representation of different reaction products and different types of antioxidant effects generated following approaches I and II [19–21]

3.4. Antioxidant activity of ENOXIL and the antioxidant interactions in the mixture with ascorbic acid

The ENOXIL is an autochthonous medicinal product obtained from grapes enotannins through slow oxidation processes [22]. The product ENOXIL possesses antiseptic and antioxidant activities, it is also a non-toxic and effective medicinal product against skin infections [22]. According to Figure 3.18, ENOXIL possesses antioxidant activity in the reaction with DPPH^{*} comparable to that of natural polyphenolic compounds [23, 24]. The EC₅₀ value for both the sample dissolved in water and for the one in phosphate buffer solution (STF) is 2.1, ENOXIL having less pronounced antioxidant properties than the rest of the tested compounds (Figure 3.14) [23, 24]. This fact proves that 2.1 g/L ENOXIL annihilates 1 g/L DPPH^{*} by 50%, and to annihilate 100% of the radical of the same concentration, 4.2 g/L ENOXIL is needed [23, 24].

Comparing these data with the antioxidant activity of the natural compounds from grapes – Cat, Que, GA, Res, it is observed that the product ENOXIL has lower antioxidant activity, since higher concentration of compound is needed to neutralize the same concentration of free radicals

[23, 24]. Expressing results in g EAA/L, it becomes possible to compare the antioxidant activities of ENOXIL samples in water and in STF as indicated in Figure 3.15 [23, 24].

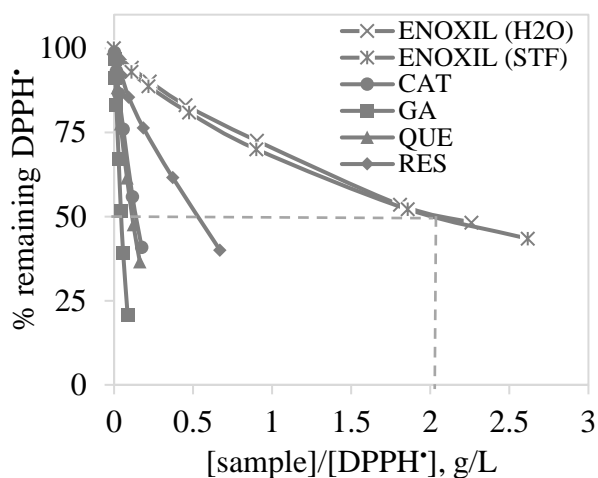


Figure 3.14. Representation of the antioxidant activity of ENOXIL dissolved in water and in STF compared to the antioxidant activity of catechin, quercetin, gallic acid and resveratrol in the reaction with DPPH* [23, 24]

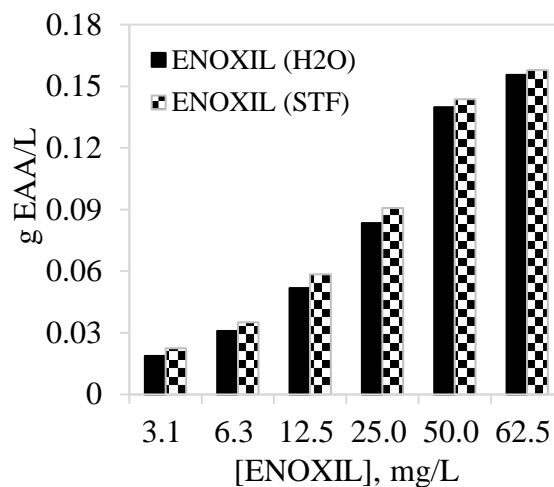


Figure 3.15. Antioxidant activity of ENOXIL in water and in STF expressed in g EAA/L in the reaction with 0.03 g/L DPPH* [23, 24]

Figure 3.15 illustrates the dependence of the antioxidant activity of ENOXIL on its concentration, demonstrating that 25.00 mg/L ENOXIL acts as 0.08 g EAA/L, 62.50 mg/L ENOXIL acts as 0.16 g EAA/L etc. [23, 24]. The difference between the data obtained in water and in STF is insignificant, with a small advantage of the results in STF; this could be due to the specificity of the DPPH* method applied [23, 24].

In the reaction with ABTS^{•+}, the ENOXIL preparation shows increased antioxidant activity (Figure 3.16). The two ENOXIL samples demonstrate higher antioxidant activity than the natural grape compound – Res [23, 24]. Comparing the two samples of ENOXIL (in water and in STF), it can be seen that the sample dissolved in STF possesses significantly higher antioxidant activity, having the index EC₅₀ = 0.06, compared to EC₅₀ = 0.14 for the sample in water [23, 24]. This fact shows that in STF less ENOXIL is needed for the annihilation of the same amount of free radical, respectively, in this environment the capture of free radicals by the preparation ENOXIL is more effective [23, 24].

Figure 3.17 demonstrates the difference in g ETrolox/L between the antioxidant activity of ENOXIL in water and in STF in the reaction with ABTS^{•+}. It is clearly observed that in STF the antioxidant activity of the preparation is twice as high as in water, for example, for the concentration of 105.60 mg/L ENOXIL the antioxidant activity is 0.28 g ETrolox/L in water, and

0.70 g ETrolox/L in STF [23, 24].

The Folin-Ciocalteu test (Figure 3.18) confirmed the antioxidant activity of ENOXIL and strengthened the idea that in STF the given product is more active than in water, for example, for the concentration 140.80 mg/L an antioxidant activity of 5.30 mg EAG/L in water and 7.50 mg EAG/L in STF was recorded. Also, with the increase in the concentration of ENOXIL, the difference between the antioxidant activity of the samples dissolved in water and in STF also increases [23, 24].

Figure 3.19 confirms the increased ability of ENOXIL to reduce Fe(III) determined by the PRFe method [23, 24].

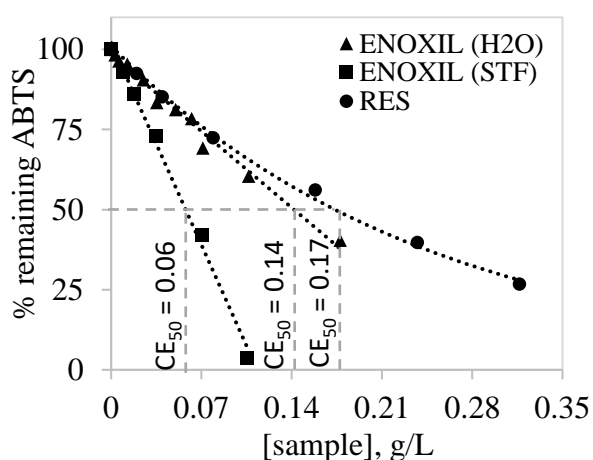


Figure 3.16. Representation of EC₅₀ values for ENOXIL in water and STF, and for Res in the reaction with ABTS^{•+} [23, 24]

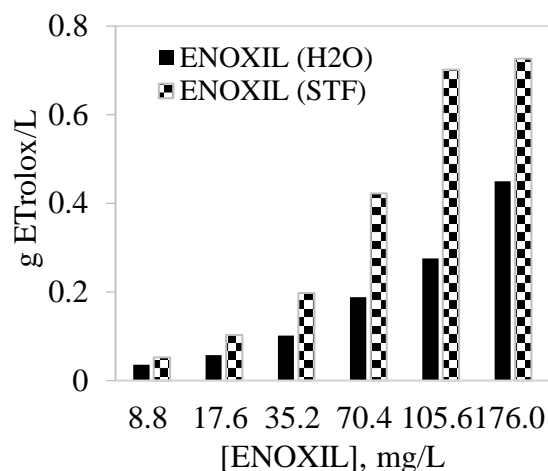


Figure 3.17. Antioxidant activity of ENOXIL in water and STF expressed as g ETrolox/L [23, 24]

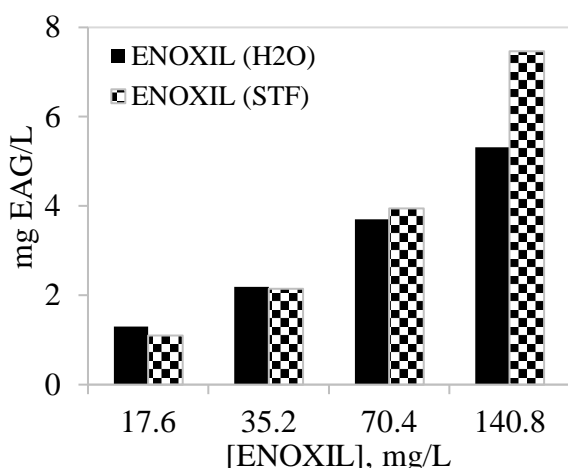


Figure 3.18. Results expressed in mg EAG/L of the Folin-Ciocalteu test for determination of antioxidant activity of ENOXIL in water and STF [23, 24]

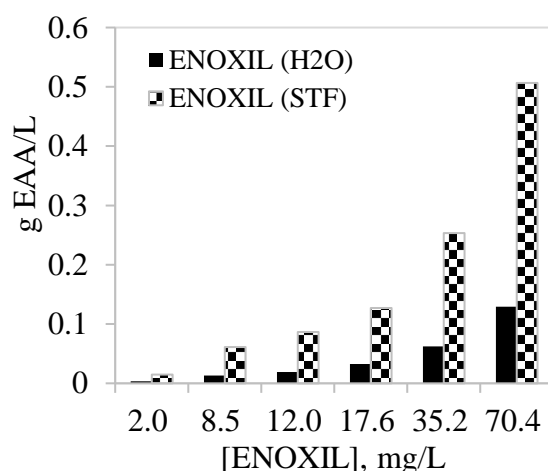


Figure 3.19. The pro-oxidant activity of ENOXIL in water and STF expressed in g EAA/L [23, 24]

In particular, significant activity is shown by the sample dissolved in STF, which has a

pro-oxidant capacity three times higher than the sample in water: for the maximum analysed concentration of 70.40 mg/L ENOXIL – 0.13 g EAA/L in water and 0.51 g EAA /L in STF [23, 24]. The increased antioxidant activity of the ENOXIL preparation in STF may be due to the fact that polyphenolic compounds are more susceptible to oxidation at basic pH.

Antioxidant interactions between ENOXIL and ascorbic acid. Antioxidant interactions between ENOXIL and AA were determined following three ways of performing the experiment: Ist (mixing AA and ENOXIL, then adding DPPH^{*}), IInd (interaction of ENOXIL with DPPH^{*}, followed by addition of AA) and IIIrd approach (the interaction of AA with DPPH^{*}, followed by the addition of ENOXIL) The data from Figure 3.20 show that all three approaches exhibit a synergistic effect, however approach II possesses the strongest synergistic interaction with a value of 1.19; Ist an IIIrd approaches possess similar synergistic effect of 1.06 and 1.07 [23, 24].

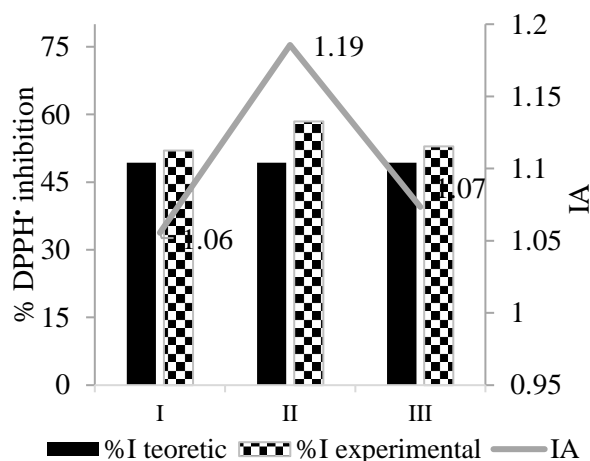


Figure 3.20. Antioxidant activity of ENOXIL – AA combinations (0.0002N) in water: Ist (ENOXIL-AA-DPPH^{*}), IInd (ENOXIL-DPPH^{*}-AA) and IIIrd approach (AA-DPPH^{*}-ENOXIL) [23, 24]

4. ECOVALEOLOGICAL CONCEPTS DEVELOPMENT AT THE ECOLOGICAL CHEMISTRY DISCIPLINE

4.1. Relationship between the study of antioxidant interactions and the concept of valeology

This subchapter argues the connection between ecovaleology and the study of antioxidant interactions. Valeology, as a scientific direction, interconnects with the study of antioxidant interactions through ecovaleology, which investigates changes in human health depending on changes occurring in the environment and nature. As indicated by the data in the specialized literature, the concentrations and combinations of antioxidants can significantly influence the antioxidant-prooxidant balance, and, through it, the biochemical reactions in mitochondria, cells affecting the well-being of the body. The mitochondria's ability to generate energy is considered in valeology an indicator of the human health status. Depending on the concentration of antioxidants, in the mitochondria can be generated reactions that result in oxidative, reductive stress or pro-oxidant effects. The concentrations of antioxidants in dietary supplements and natural products are different, this fact distinctly affects the antioxidant interactions between the

constituent compounds. In this context, the relationship between mitochondria - antioxidants - ecovaleology - health takes shape even better, taking into account the positive or negative impact that antioxidants can have in mitochondria - by affecting/regulating the redox balance in the intracellular environment.

4.2. Development of students' ecovaleological concepts - sustainable approach in solving ecological problems

Integration of the ecovaleology concept in the content of the lecture "Food chemistry and product quality assurance. Antioxidants" of the Ecological Chemistry course at the Moldova State University offered a new vision on antioxidants and antioxidant interactions. The presentation and argumentation of the scientific results obtained within the Institute of Chemistry of MSU favoured students' familiarization with the topic of antioxidant interactions, the pro-oxidant character of compounds, the importance of the concentration of antioxidants, the reaction mechanism. The mentioning of health benefits and risks of antioxidant consumption, their concentration and combination facilitated the integration of ecovaleological principles into the content of the lecture.

According to the results of the elaborated questionnaire [25], students demonstrate a positive attitude towards the consumption of antioxidants. The didactic materials presented strengthened the knowledge regarding natural sources rich in antioxidants, redox reactions, the importance of antioxidant consumption, causes of radical species formation. After the lecture, 90% of students pleaded for the consumption of antioxidants from natural sources and only 6.7% people chose "food additives" option; 56.7% of students do not consider food supplements more effective than antioxidants from natural sources; 95% of young people believe that consuming a high concentration of a single antioxidant "is dangerous for health", the choice of this option being due to approaching the problem of the pro-oxidant nature of antioxidants during the lecture [25].

4.3. Integration of the ecovaleology concept into the curriculum of the Ecological Chemistry discipline

In order to facilitate students' familiarization with the ecovaleology concept, chemical reaction schemes, diagrams, representative images useful for the topic have been presented during the lecture. The subject of ecovaleology was treated in a subtle way, at each objective of the lecture, emphasizing the importance of nutrients for maintaining health, the negative influence on health of pollutants and free radicals generated by pollutants, the beneficial or harmful effect of antioxidants depending on their concentration etc. Special attention was given to the interactions between antioxidants, a subject that was exemplified through the presentation of the current results reported in the specialized literature and the experimental data obtained in the Laboratory of Physical and Quantum Chemistry of the Institute of Chemistry of MSU.

CONCLUSIONS AND RECOMMENDATIONS

1. The content of phenolic compounds and organic acids in the autochthonous grape varieties – Copceac, Feteasca Neagră, Viorica, Riton, varies considerably depending on the ripening stage: unripe, at veraison and ripe berries. The obtained results demonstrate a regular dynamic of the basic physico-chemical indicators, of the content of major organic acids (max. 15 – 22 g/L in unripe grapes, min. 1 – 8 g/L in ripe grapes), of phenolic compounds (from 3.94 g EAG/L in unripe grapes, up to 2.05 g EAG/L in ripe ones), proanthocyanidins (unripe grapes – 1 g ECat/L, ripe berries – 0.39 g ECat/L) and anthocyanins (at veraison grapes – 411.23 mg EMalv/L, ripe grapes – 784.78 mg EMalv/L). These variations that are dependent on the ripening period and grape variety, significantly influence their quality and antioxidant properties.
2. The DPPH[•], ABTS^{•+}, PRFe tests were applied for the determination of the antioxidant activity. It was established that the antioxidant activity of analysed grape varieties is consistent with the changes in the phenolic compounds' content. The highest values of 2.19 g EAA/L (DPPH[•] method), 8.11 g ETrolox/L (ABTS^{•+} method), 4.07 g EAA/L (PRFe method) have been recorded in unripe grape samples due to the high total content of phenolic compounds, including proanthocyanidins, in berry pulp.
3. For the determination of antioxidant interactions between natural compounds, optimum concentration ratios, similar to those found in grapes, in terms of combination and concentration, have been established. Thus, in mixtures with tartaric or citric organic acids, the concentration ratios studied vary for each compound – ascorbic acid: 1 – 700, gallic acid: 1 – 2500, catechin: 1 – 1000, quercetin: 1 – 800, rutin: 1 – 900 and resveratrol: 1 – 5000; and in mixtures with dihydroxyfumaric acid, the ratios are in the range of 0.05 – 10
4. At low concentrations of phenolic compound, strong antagonistic effects were recorded in most of the studied samples (min. 0.28); increasing the concentration of the phenolic compound results in additive (≈ 1) or synergistic effects (>1). Augmenting the concentration of tartaric or citric acids does not significantly affect the type of antioxidant interactions, except for resveratrol–tartaric or citric acid mixtures. Contrary to the given fact, increasing the concentration of dihydroxyfumaric acid affects the type of antioxidant interactions, favouring the manifestation of synergistic effects in the mixtures of ascorbic acid (max. 1.17) and rutin (max. 1.07); increasing the concentration of dihydroxyfumaric acid in samples with catechin, diminishes the synergistic effects and causes the appearance of additive and antagonistic ones (min. 0.89); in samples with gallic acid, quercetin or resveratrol, the concentration of dihydroxyfumaric acid did not generate significant variations of the type of antioxidant interaction.

5. Antioxidant interactions between phenolic compounds and tartaric and citric organic acids are predominantly antagonistic (0.28 – 0.94), especially in the samples with quercetin and resveratrol. It was established that the antagonistic effect is caused by the presence of high concentrations of organic acid ions in the reaction medium, which leads to the inhibition of the SPLET mechanism of action of phenolic compounds. In the mixtures with gallic acid or catechin, multiple additive effects were observed (0.95 – 1.04); exception were samples containing rutin and tartaric or citric acid that demonstrated strong synergistic effects of max. 1.27 and 1.29 respectively. The manifestation of synergistic effects can be caused by oligomerization processes of phenolic compounds, a phenomenon that can result in formation of new structures with increased antioxidant capacity.

6. Data obtained in mixtures of a phenolic compound and dihydroxyfumaric acid reveal the presence of synergistic, additive and antagonistic antioxidant effects. Mixtures of dihydroxyfumaric acid and catechin or rutin show the highest synergistic effect of 1.08 and 1.07, respectively, due to potential polyphenol oligomerization reactions. The quercetin - dihydroxyfumaric acid combination mainly demonstrates additive antioxidant interactions in the range of 0.95 - 0.99, and the mixtures of gallic acid - dihydroxyfumaric acid and resveratrol - dihydroxyfumaric acid show strong antagonism, registering minimum values of 0.43 and 0.75, respectively.

7. In mixtures of ascorbic and tartaric acids, moderate synergistic effects have been established, the maximum values being 1.08. For ascorbic acid - citric acid mixtures, the predominance of additive effects has been observed (0.95 – 1.04). The presence of synergistic and additive interactions is due to the high concentration of tartaric or citric acid ions in the reaction, which supports the HAT mechanism of action of ascorbic acid.

8. The presence of strong synergistic effects between ascorbic and dihydroxyfumaric acids was determined by adapting and applying four spectral analysis methods – UV-Viz, Stopped-Flow, RES and NMR. The data obtained by UV-Vis spectroscopy demonstrates synergistic effects in the range of 1.05 – 1.17, noticed at the maximum concentrations of the tested compounds. The Stopped-Flow spectroscopy results indicates on an increase of the reaction speed (10 times in the case of dihydroxyfumaric acid and 2 times in the case of ascorbic acid) and on the enhancement antioxidant activity of the analysed acids in wine matrix compared to the results obtained in 98% ethanol. RES spectroscopy data demonstrates the existence of strong (1.24) and moderate (0.9 – FIC method) synergistic effects between ascorbic and dihydroxyfumaric acids, two different calculation methods being applied. Applying NMR spectroscopy, it was established that the

synergistic antioxidant interaction is favoured by some partial regeneration processes between ascorbic and dihydroxyfumaric acids, the latter one having the ability to regenerate ascorbic acid.

9. In the ascorbic acid - resveratrol mixture there are antagonistic and synergistic antioxidant effects depending on the order of compounds' addition to the reaction. The maximum synergistic effect of 1.19 is obtained when resveratrol is initially added to the DPPH[•] solution, and after the complete consumption of stilbene, ascorbic acid is added. NMR spectra demonstrated that this scenario results in the formation of *trans*- δ -viniferins, which possess antioxidant activity and enhance the synergistic effect of the mixture of compounds.

10. In a phosphate buffer solution, ENOXIL has 2-3 times higher antioxidant activity than in water. By adding ascorbic acid to the ENOXIL solution, the results demonstrate the presence of synergism in all samples analysed. The total antioxidant activity and the magnitude of the synergistic effect depend on the order of compounds' addition to the reaction, so the highest synergistic effect – 1.19, was obtained when ENOXIL initially interacts with DPPH[•], then ascorbic acid is added.

11. Approaching the study of antioxidant interactions from the ecovaleological perspective offers a new view on this subject. Integration of the ecovaleology concept in the content of the lecture "Food chemistry and product quality assurance. Antioxidants" of the Ecological Chemistry course at the Moldova State University allowed students to become familiar with the advantages and risks for health of antioxidants' consumption, the effect of the concentration of these compounds on health, facilitated the argumentation of the benefit of the consumption of antioxidants from natural sources, also oriented students towards an ecological lifestyle that resonate with the sustainable development of society. The elaborated questionnaire demonstrated that the lecture had a positive impact on the interpretation of the didactic material and on the formation of conclusions regarding the consumption of antioxidants, the impact of the concentration of the given compounds and the importance of antioxidants for health.

Recommendations

- It is recommended to apply the scientific results obtained to improve the antioxidant effect and the efficiency of food, cosmetic, medicinal, pharmacological products and existing technological processes.
- It is recommended to introduce the concept of ecovaleology into the curriculum of the Ecological Chemistry course at Moldova State University for the formation of healthy, ecological and sustainable skills among young people.

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ADNOTARE

Vicol Crina, „Interacțiuni antioxidante dintre unii compuși fenolici și acizi organici din struguri – contribuție la formarea ecovaleologică a tinerilor specialiști”, teză de doctor în științe chimice, Chișinău, 2024

Structura tezei. Teza este formată din introducere, cinci capitole, concluzii generale și recomandări, bibliografia din 269 surse, 59 figuri, 8 tabele și 4 anexe, 128 pagini text de bază. Rezultatele obținute sunt publicate în 26 lucrări științifice.

Cuvinte-cheie: antioxidant, compuși fenolici, acizi organici, interacțiuni antioxidante, efect sinergic, efect antagonist, efect aditiv, struguri, ecovaleologie.

Domeniul de studiu: 145.01 Chimie Ecologică

Scopul și obiectivele tezei constau în determinarea (i) tipului de interacțiune antioxidantă dintre unii compuși fenolici și acizi organici din struguri și (ii) a dependenței efectelor antioxidante de concentrația și combinația substanțelor investigate; (iii) formularea unor concluzii privind consumul și utilizarea eficientă a antioxidantilor.

Noutatea și originalitatea științifică. În premieră au fost determinate tipurile de interacțiuni antioxidante dintre unii compuși fenolici și acizi organici naturali, fiind studiate combinațiile și concentrațiile similare celor din struguri. Au fost propuse mecanismele de interacțiune antioxidantă pentru amestecurile studiate: compus fenolic – acid organic, acid ascorbic – acid dihidroxifumaric, acid ascorbic – resveratrol. În premieră au fost aplicate metodele DPPH[•], ABTS^{•+} și PRFe pentru studierea activității antioxidante a soiurilor de struguri autohtoni de selecție nouă. Pentru prima dată, subiectului interacțiunilor antioxidante a fost abordat din perspectiva conceptului de ecovaleologie în scopul formulării concluziilor privind consumul rațional și întrebuintarea eficientă a antioxidantilor.

Problema științifică soluționată rezidă în identificarea efectelor antioxidante existente între compușii fenolici și acizii organici din struguri, fapt care relevă avantajele consumului antioxidantilor din surse naturale sau în combinații și concentrații similare, și servește drept soluție pentru caracterul prooxidant al compușilor antioxidanți.

Semnificația teoretică. Rezultatele obținute îmbogățesc și completează studiile existente, de asemenea, permit formularea unor idei mai exacte referitoare la mecanismele și procesele redox în care pot fi implicate substanțele studiate – procese care au loc în struguri, vinuri, precum și în organismul uman odată ce compușii dați sunt consumați cu hrana. De asemenea, datele obținute argumentează importanța concentrației, a mediului de reacție și a consecutivității adăugării compușilor în reacție asupra activității antioxidante totale și tipului de interacțiune antioxidantă. Rezultatele investigației aduc un aport științific și didactic privind formarea ecovaleologică a tinerilor în instituțiile de învățământ superior.

Valoarea aplicativă se axează pe posibilitatea utilizării concluziilor elaborate în baza datelor experimentale pentru îmbunătățirea efectului antioxidant și a eficienței produselor farmaceutice, cosmetice și a procedurilor tehnologice existente. Totodată, rezultatele obținute pot fi ușor integrate în conținutul cursurilor didactice la disciplinele chimie, chimie ecologică, ecologie etc.

Implementarea rezultatelor științifice. Rezultatele obținute au fost integrate și prezentate, timp de patru ani consecutivi, în cadrul prelegerii „Chimia alimentară și asigurarea calității produselor. Antioxidanții” ce face parte din cursul de Chimie ecologică condus de acad. Gh. Duca la Universitatea de Stat din Moldova.

ANNOTATION

Vicol Crina, "Antioxidant interactions between some grape phenolic compounds and organic acids - contribution to the ecovaleological education of young experts", PhD thesis in chemical sciences, Chisinau, 2024

Thesis structure. The thesis consists of the introduction, five chapters, general conclusions and recommendations, the bibliography of 269 sources, 59 figures, 8 tables and 4 appendices, 128 pages of basic text. The results obtained are published in 26 scientific works.

Key words: antioxidant, phenolic compounds, organic acids, antioxidant interactions, synergistic effect, antagonistic effect, additive effect, grapes, ecovaleology.

Field of study: 145.01 Ecological Chemistry

The purpose and objectives of the thesis are to determine (i) the type of antioxidant interactions between some grape phenolic compounds and organic acids and (ii) the dependence of the antioxidant effects on the concentration and combination of the investigated substances; (iii) to formulate conclusions regarding the consumption and effective use of antioxidants.

Scientific novelty and originality. For the first time, the types of antioxidant interactions between some natural phenolic compounds and organic acids have been determined, by studying the combinations and concentrations similar to those in grapes. Antioxidant interaction mechanisms were proposed for the studied mixtures: phenolic compound – organic acid, ascorbic acid – dihydroxyfumaric acid, ascorbic acid – resveratrol. For the first time, the DPPH[•], ABTS^{•+} and PRFe methods were applied to study the antioxidant activity of autochthonous grape varieties of new selection. A new perspective on the topic of antioxidant interactions was offered by addressing the subject from the view of the ecovaleology concept in order to formulate conclusions regarding the consumption and efficient use of antioxidants.

The **solved scientific problem** resides in the identification of the existing antioxidant effects between grape phenolic compounds and organic acids, a phenomenon that reveals the advantages of consumption of antioxidants from natural sources or in similar combinations and concentrations, and serves as a solution for the prooxidant character of antioxidant compounds.

Theoretical significance. The obtained results enrich and complement the existing studies, also allow the formulation of more accurate ideas regarding the redox mechanisms and processes in which the studied substances can be involved - processes that take place in grapes, wines, as well as in the human body once the given compounds are consumed with food. Also, the obtained data argue the importance of the concentration, reaction environment and consecutiveness of compounds addition in the reaction on the total antioxidant activity and the type of antioxidant interaction. The results of the investigation bring a scientific and didactic contribution regarding the ecovaleological training of young people in higher education institutions.

The **applicative value** relies on the possibility of using the conclusions developed based on experimental data to improve the antioxidant effect and the efficiency of pharmaceutical, cosmetic products and the existing technological processes. At the same time, the obtained results can be easily integrated into didactic courses of chemistry, ecological chemistry, ecology disciplines.

Implementation of scientific results. The obtained results were integrated and presented, four consecutive years, within the lecture "Food chemistry and product quality assurance. Antioxidants" which is part of the Ecological Chemistry course taught by acad. Gh. Duca at the State University of Moldova.

АННОТАЦИЯ

Викол Крина, «Антиоксидантные взаимодействия между некоторыми фенольными соединениями винограда и органическими кислотами – вклад в эковалеологическое образование молодых специалистов», диссертация по на соискание ученой степени доктора химических наук, Кишинев, 2024 г.

Структура диссертации. Диссертация состоит из введения, пяти глав, общих выводов и рекомендаций, библиографии из 269 источников, 59 рисунков, 8 таблиц и 4 приложений, 128 страниц основного текста. Полученные результаты опубликованы в 26 научных работах.

Ключевые слова: антиоксидант, фенольные соединения, органические кислоты, антиоксидантные взаимодействия, синергетический эффект, антагонистический эффект, аддитивный эффект, виноград, эковалеология.

Область исследования: 145.01 Экологическая химия

Цель и задачи диссертационной работы заключаются в определении: (i) типа антиоксидантных взаимодействий между некоторыми фенольными соединениями и органическими кислотами в винограде и (ii) зависимости антиоксидантного действия от концентрации и сочетания исследуемых веществ; (iii) формулирование выводов относительно потребления и эффективного использования антиоксидантов.

Научная новизна и оригинальность. Впервые были определены типы антиоксидантных взаимодействий между некоторыми фенольными соединениями и природными органическими кислотами, исследуемыми в сочетаниях и концентрациях, аналогичных таковым в винограде. Предложены механизмы антиоксидантного взаимодействия исследуемых смесей фенольных соединений и органических кислот. Впервые методы DPPH[•], ABTS^{•+} и PRFe были применены для изучения антиоксидантной активности автохтонных сортов винограда новой селекции. Впервые была рассмотрена тема антиоксидантных взаимодействий с позиций эковалеологической концепции с целью формулирования выводов об рациональном потреблении и эффективном использовании антиоксидантов.

Решенная научная проблема заключается в выявлении существующих антиоксидантных эффектов между фенольными соединениями и органическими кислотами из винограда, что раскрывает преимущества потребления антиоксидантов из природных источников или в аналогичных комбинациях и концентрациях и служит решением проблемы прооксидантного характера антиоксидантных соединений.

Теоретическое значение: Полученные результаты обогащают и дополняют существующие исследования, а также позволяют сформулировать более точные представления относительно окислительно-восстановительных механизмов и процессов, в которых могут участвовать изучаемые вещества. Результаты исследования вносят научный и дидактический вклад в эковалеологическую подготовку молодых специалистов.

Прикладное значение ориентировано на возможность использования выводов диссертации для повышения антиоксидантного действия и эффективности фармацевтических, косметических, а также существующих технологических процессов. Полученные результаты можно легко интегрировать в содержание дидактических курсов по дисциплинам химия, экологическая химия, экология и т.д.

Внедрение научных результатов: Полученные результаты были интегрированы и представлены на лекции «Химия пищевых продуктов и безопасность пищевых продуктов; Антиоксиданты» в рамках курса «Экологическая химия», читаемого акад. Г. Дука в Государственном Университете Молдовы.

VICOL Crina

**ANTIOXIDANT INTERACTIONS BETWEEN SOME
PHENOLIC COMPOUNDS AND ORGANIC ACIDS
FROM GRAPES – CONTRIBUTION TO THE
ECOVALEOLOGICAL TRAINING OF YOUNG
SPECIALISTS**

145.01 Ecological chemistry

Abstract of the doctoral thesis in chemical sciences

Approved for printing: 20.08.2024

Offset paper. Digital printing.

Printing sheets: 2.1

Paper size: 60×84 1/16

Copies: **35 ex.**

Order no. 65-24

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