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INVESTIGATION RELATIONSHIP BETWEEN ANTIMICROBIAL, ANTIOXIDANT ACTIVITY AND BIOLOGICALLY ACTIVE COMPOUNDS OF BLACKBERRY (*RUBUS FRUTICOCUS* L.) FRESH FRUIT LIQUID EXTRACTS

Artem Marchenko, Olexander Maslov, Mykola Komisarenko, Svitlana Ponomarenko*, Tetyana Osolodchenko*, Sergii Kolisnyk

National University of Pharmacy

***Mechnikov Institute of Microbiology and Immunology of the NAMS of Ukraine**

Introduction. The search for natural antibacterial agents has gained significant interest in recent years, driven by the growing concerns over antibiotic resistance and the desire for natural alternatives. Fresh blackberries, known for their rich nutritional profile and high antioxidant content, have attracted attention for their potential antibacterial properties. Understanding the antibacterial potential of blackberries could provide insights into their use in natural medicine and food preservation. **Material and methods.** The quantity of phenolic compounds, anthocyanins was determined by spectrophotometric method of analysis, whereas organic acids by alkalimetric method; antioxidant activity of obtained extracts was evaluated by potentiometric method, antimicrobial was determined by method of "well". **Results and Discussion.** Results demonstrates the highest amount of polyphenols, anthocyanins were 0.35±0.01, 0.29±0.02 in 96% ethanolic extract, respectively. The organic acids were dominated in aqueous and 60% EtOH extracts (0.84±0.02%). The most potent antioxidant property possessed 96% EtOH extract of blackberry fresh fruit. There is a high correlation between the content of polyphenols, antioxidant activity and inhibition of *Bacillus subtillis*, whereas antioxidant power highly depends on total polyphenols and anthocyanins. **Conclusion**. These findings show the great potential of blackberry extracts in the development and creation of new medicines with antimicrobial, antioxidant effects that are not inferior to the action of synthetic analogues.
Key words*: anthocyanins, phenolic compounds, organic acid, correlation analysis, blackberry, fresh fruit*

Introduction

Bacterial infections have played an essential role in increasing morbidity of patients [1]. Nowadays, heart attack remains the leading cause of death, however, infection diseases due to high resistance become the problem number one for contemporary medicine [2]. The widespread and uncontrolled application of antibiotics have caused such catastrophe in treatment infections of resistant pathogens. The recent study has shown that antimicrobial resistance causes 10 million deaths a year by 2050 [3]. The number of resistant pathogenic bacteria grows at high rate, especially in zone of military conflict, so search for novel antimicrobial agents from medicinal plants to combat resistant pathogens has become a crucial for today [4].

Today, medical plants that are rich source of anthocyanins have a high attention from scientific community [5]. Above all, it relates with fact that some resistance pathogens are more sensitive to natural products, secondly, natural compounds have potent antioxidant effect and moreover, the side effects are rarely happened after application of natural compounds than after synthetic drugs.

The perspective source of anthocyanins was chosen blackberry fruits. Blackberry (*Rubus fruticosus* L.) is a shrub of the *Rosacea* family. The distribution area is Europe, North America, Asia [6]. The chemical composition of *R. fruticosus* fruits is represented by anthocyanins (cyanidine-3-O-glucoside), organic acids (citric acid) and hydroxycinnamic acids (caffeic acid) [7].

There are a lot of numbers of research about investigation pharmacological activity of *R. fruticosus* fruit. It is known that anthocyanins from *R. fruticosus* fruit, possess: anti-inflammatory, antimicrobial, anti-hyperglycemic, immune-modulation, and anticancer effects. Besides, in folk medicine *R. fruticosus* are traditionally applied to treat fever, infections, diabetes, and liver diseases [8]. In our view, the anthocyanins are perspective for the development of new antimicrobial, and antioxidant pharmaceuticals.

There are a lot of scientific researches about determination a level antioxidant activity of *R. fruticocus* fresh fruit extracts [9, 10, 11]. However, there is no date about assessing antioxidant\antimicrobial activity and its correlation with content of BAS by potentiometric method. So, the aim of the study was to determine the total content of polyphenols, anthocyanins, and organic acids, moreover study antimicrobial activity against *Staphylococcus aureus*, *Proteus vulgaris*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and fungi *Candida albicans*. In addition, it was aimed to study a correlation analysis between the content of BAS in *R. fruticocus* fresh fruit extracts and antimicrobial, antioxidant activity.

Material and methods

R. fruticocus fruits were the object of the study, which were collected in the places of its cultivation. The material was collected in 2021 during the fruiting period in the vicinity of the village of Ternova, Kharkiv region.

The pH meter HANNA 2550 (Germany) with a combined platinum electrode EZDO 50 PO (Taiwan) was applied for potentiometric measurements. Quantitative analysis of biological active compounds was carried out on UV-spectrophotometer UV – 1000 (China) with matched 1 cm quarts cells. Weighing was carried out using digital analytical balance AN100 (AXIS, Poland) with d = 0.0001 g. A six samples of 10.0 g (exact mass) of *R. fruticocus* fresh fruits had the size of particles 1-2 mm. The extraction was conducted with distilled water, 20%, 40%, 60%, 96% ethanol at 80º C within 1 hour with a condenser, ratio raw material/solvent – 1/20. The extraction technique was completed twice to provide totally extract all BAS, then the filtrates were joint and evaporated by vacuum rotary to ratio of extract to raw material 1:2. The six extracts of 96, 60, 40, 20% EtOH and aqueous were obtained. The green

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tea (*Camellia sinensis* L.) extract was obtained by the mentioned above method with 60% ethanol.

The total content of phenolic compounds was measured by the Folin-Ciocaltau assay, the absorbance was measured at 760 nm [12]. The total anthocyanin content was determined by the molecular adsorption analysis, the absorbance was measured at 546 nm [12]. The total organic acids content was determined by acid-base titration with the fixation end-point by potentiometric method [13].

Antioxidant activity of extract was evaluated by potentiometric method [14, 15].

The standardized green tea leaf 60% extract was used as the reference drug.

Strains of *Staphylococcus aureus ATCC 25923*, *Pseudomonas aeruginosa ATCC* 27853, *Escherichia coli ATCC 25922*, *Bacillus subtillis ATCC 6538*, *Proteus vulgaris NTCS 4636*, and *Candida albicans ATCC 885/653* were used in accordance with the recommendations for the assessment of antimicrobial activity of drugs**.**

The method of diffusion of the drug into agar carried out using the method of "wells" [16, 17]. Gentamycin, and fluconazole were used as reference drugs for assessing antimicrobial and anti-fungal activity."

Pearson's (r) correlation coefficient was used to analyze the correlation between antioxidant activity and the amount of phenolic, anthocyanins and organic acids. The correlation coefficient to takes a value in the range of -1 to +1. Correlation is very high if it is within the range from 0.90 to 1.00; from 0.70 to 0.90 is a high correlation; from 0.50 to 0.70 is a moderate correlation; from 0.30 to 0.50 is a low correlation; from 0.00 to 0.30 negligible correlation [18]

Results and discussion

According to obtained results shown in Table 1, the 96% EtOH extract (0.35±0.01%) had the most significant amount of phenolic compounds, followed by 60% EtOH extract (0.28±0.02%), whereas the lowest one – aqueous extract (0.17±0.01%).

The content of anthocyanins increasing in the following order aqueous extract (0.15±0.02%) > aqueous extract (0.73±0.01%) > 40% EtOH extract (0.17±0.02%) > 60% EtOH extract (0.20±0.01%) > 20% EtOH extract (0.16±0.02%). The percentage of catechins out of total of polyphenols was 53, 54, 63, 50 and 54% for 96%, 60%, 40%, 20% and aqueous extracts, respectively. The highest percentage of catechins was in 40% extract, whereas the lowest in 20% extract. (Table 1)

The highest content of organic acids was determined in aqueous extract (0.84±0.02%), followed by 60% EtOH extract (0.84±0.01%), whereas the lowest one in 96% EtOH extract (0.56±0.01%). The total content of organic acids was lower 153%, 110%, 48%, 32% than content in 96%, 60%, 40%, 20% extracts, respectively. (Table 1)

Table 1. The total phenolic compounds, anthocyanins and organic acids in R. fruticocus fresh fruit liquid extracts

Sample	Dry residue, %±SD[a]	Total phenolic compounds content expresses as gallic acid, %±SD[a]	Total anthocyanins content expressed as cyanidine-3-O-glucoside, %±SD[a]	Total organic acids expressed as citric acid, %± SD[a]
96% EtOH extract	2.07±0.02	0.35±0.01	0.29±0.02	0.56±0.01
60% EtOH extract	2.38±0.02	0.28±0.02	0.20±0.01	0.84±0.01
40% EtOH extract	3.42±0.03	0.21±0.02	0.17±0.02	0.77±0.01
20% EtOH extract	3.60±0.03	0.18±0.02	0.16±0.02	0.72±0.02
Aqueous extract	3.85±0.03	0.17±0.02	0.15±0.02	0.84±0.02

[a]Standard deviation, n=5

A potentiometric method for determining antioxidant activity was used to evaluate the effect of the obtained extracts of *R. fruticocus* fresh fruit. Table 2 shows that the level of antioxidant activity increases in the following order: aqueous extract (12.49±0.12 mmol-eqv./$m_{dry\ res.}$) > 20% EtOH extract (12.62±0.13 mmol-eqv./$m_{dry\ res.}$) > 40% EtOH extract (13.05±0.13 mmol-eqv./$m_{dry\ res.}$) > 60% EtOH extract (17.40±0.17 mmol-eqv./$m_{dry\ res.}$) > 96% EtOH extract (22.29±0.22 mmol-eqv./$m_{dry\ res.}$) . In light of the data obtained, it can be established that the 96% EtOH extract has the highest level of antioxidant activity. According to the modern classification of antioxidant activity, which was previously developed in our previous research [19], it was found that all extracts obtained have a high level of antioxidant activity.

Table 2. The level of antioxidant activity of *R. fruticocus* fresh fruit liquid extracts

Sample	Antioxidant activity, mmol-eqv./$m_{dry\ res.}$ ±SD[a]	Conditional term of antioxidant level
96% EtOH extract	22.29±0.22	Medium level
60% EtOH extract	17.40±0.17	Lower Medium level
40% EtOH extract	13.05±0.13	Lower Medium level
20% EtOH extract	12.62±0.13	Lower Medium level
Aqueous extract	12.49±0.12	Lower Medium level
Green tea leaf 60% extract	548.79±10.98	Very high level

[a]Standard deviation, n=5

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Table 3. Comparing the value of antioxidant activity of *R. fruticocus* fresh fruit liquid extracts with *C. sinensis* leaf 60% extract at the concentration 0.01 mol/L expressed in the total phenolic compounds as gallic acid

Sample	Concentration of polyphenols, mol/L	Antioxidant activity, mmol-eqv./$m_{dry\ res.}$ ±SD[a]
96% EtOH extract	0.01	11.15±0.11
60% EtOH extract		10.90±0.11
40% EtOH extract		10.90±0.11
20% EtOH extract		12.62±0.13
Aqueous extract		12.49±0.13
Green tea leaf 60% EtOH extract		9.50±0.10

[a]Standard deviation, n=3

Moreover, a comparative analysis of the "strength" of antioxidant activity was carried out with the gold standard 60% EtOH extract of *C. sinensis* leaf. The *C. sinensis* leaf extract was obtained by the same technological method as *R. fruticocus* fresh fruit extracts. The obtained extracts were significantly inferior in antioxidant effect to *C. sinensis* leaf extract. Further, a 0.01 mol/L solutions (in terms of the amount of polyphenols expressed as gallic acid) of extracts of *v* and *C. sinensis* leaf were prepared. As a result of the study, it was found that when compared at the same concentrations, the 20% EtOH extract had the highest antioxidant effect, and the least – 60% and 40% EtOH extract. (Table 3)

In this research work, the antimicrobial activity of the obtained *R. fruticocus* fresh fruit extracts was investigated against the following strains of *S. aureus*, *B. subtilis*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, as well as a strain of the fungus *C. albicans*. According to the obtained results, all extracts obtained from the *R. fruticocus* fresh fruit had an effective antimicrobial effect. (Table 4)

S. aureus was most sensitive to the 60% EtOH extract (18.0 ± 0.4 mm) and least sensitive to the aqueous extract (14.0 ± 0.6 mm). When comparing the results of the gentamicin standard and the 60% EtOH extract, it was found that the 60% EtOH extract was 18% lower at inhibiting the growth of the *S. aureus* strain of bacteria. According to the results presented in Table 4, *B. subtilis*, as well as *S. aureus*, was highly sensitive to the 96 and 60% EtOH extract (17.0 ± 0.4 mm), followed by 40% EtOH extract (16.0 ± 0.4 mm), and the aqueous and 20% EtOH extracts inhibited the growth of the bacterial strain the least (15.0±0.5 mm). *E. coli* was the most sensitive to the action of 60% EtOH extract, in the second place – 40% EtOH extract, whereas *P. aeruginosa* and *P. vulgaris* were sensitive to 96 and 60% EtOH extracts. (Table 4)

When studying antifungal activity against *C. albicans*, the results showed that 60% extract of *R. fruticocus* fresh fruit was the most actively inhibited the growth of the fungus, whereas aqueous extract was the least active inhibited the growth of fungi. When compared with the fluconazole standard, it was found that the 60% extracts inhibited fungal growth 30% lower than fluconazole. (Table 4) The studied *R. fruticocus* fresh fruit extract showed antimicrobial activity against the following strains of *S. aureus*, *P. aeruginosa*, *P. vulgaris*, *B. subtillis* and *C. albicans*. According to the obtained data, at first glance it can be considered that the antimicrobial activity of *R. fruticocus* fresh fruit extracts is significantly inferior to the action of gentamicin and fluconazole, because their concentration of solutions was lower than the content of polyphenols in the extract. However, we would like to note that gentamicin has serious toxicity to the auditory nerve, kidneys and liver, which can lead to serious complications of the disease.

Table 4. The value of antimicrobial activity of *R. fruticocus* fresh fruit liquid extracts

Sample	Concentration mmol/L, (expressed in total polyphenols as gallic acid)	Diameter of the growth retardation zone, mm±SD[a]					
		Gramm-positive		Gramm-negative			Fungi
		Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Proteus vulgaris*	*Pseudomonas aeruginosa*	*Candida albicans*
96% EtOH extract	0.006	17.0±0.4	17.0±0.4	15.0±0.5	16.0±0.4	16.0±0.4	13.0±0.6
60% EtOH extract	0.005	18.0±0.4	17.0±0.4	18.0±0.4	16.0±0.5	16.0±0.5	14.0±0.6
40% EtOH extract	0.004	17.0±0.4	16.0±0.4	16.0±0.4	15.0±0.4	15.0±0.4	13.0±0.6
20% EtOH extract	0.003	16.0±0.5	15.0±0.5	15.0±0.5	15.0±0.5	15.0±0.5	12.0±0.6
Aqueous extract	0.003	14.0±0.6	15.0±0.5	13.0±0.6	13.0±0.6	13.0±0.6	12.0±0.6
Gentamycin	0.003	22.0±0.3	24.0±0.3	25.3±0.3	25.0±0.3	25.7±0.3	12.0±0.6
Fluconazole	0.003	18.0±0.4	12.0±0.7	14.3±0.6	12.3±0.3	10.0±0.7	20.0± 0.3

The dependence of antioxidant, antimicrobial and antifungal activity on the content of different groups of BAS was studied using the method of linear regression. In Fig. 1 shows that the correlation between the antioxidant effect and the content of polyphenols was very high (R=0.9863), in the case of anthocyanins was very high (R=0.9804), and the lowest correlation value was observed for organic acids.

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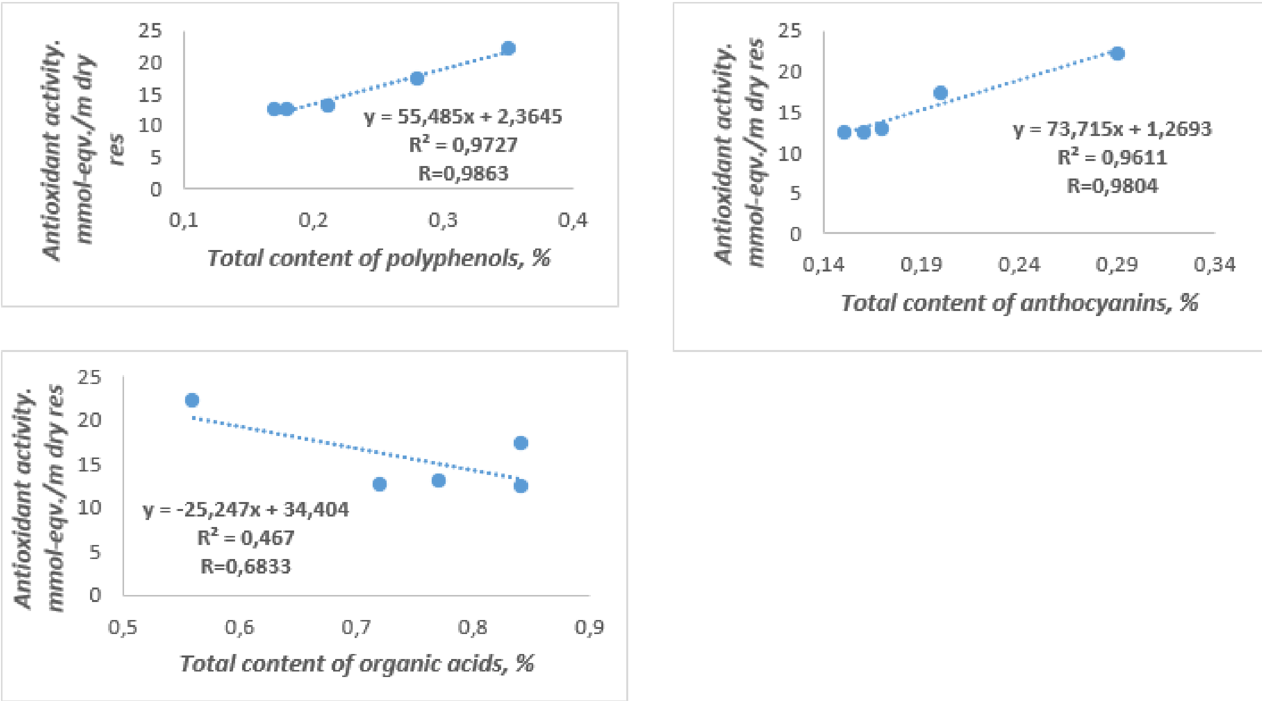

Figure 1. Correlation relationship between value of antioxidant activity and total content of polyphenols, anthocyanins, organic acids

According to the research results presented in Fig. 2 it was found that there is a moderate correlation between phenolic compounds (R=0.6596), antioxidant activity (R=0.5408) and inhibition of the growth of *S. aureus*, while in the case of anthocyanins (R=0.1356) and organic acids (R=0.2309) there is no correlation.

In Fig. 3 shows that the antibacterial effect against *B. subtilis* is very highly dependent on the content of polyphenols acids (R=0.9215), high dependent on antioxidant activity (R=0.8529), in turn, the content of organic acids and anthocyanins there is no dependence.

The study showed that there is a low correlation between phenolic compounds (R=0.4239), anthocyanins (R=0.4604), and inhibition of *E. coli* growth, while organic acids, antioxidant activity are not effect on the growth inhibition of *E. coli*. (Fig. 4)

When studying the relationship between inhibition of growth of *P. vulgaris* and the content of different groups of BAS, it was found that there is a high dependence of antibacterial activity on the amount of polyphenols (R=0.7793), antioxidant activity (R=0.7026), in turn, anthocyanins had not correlation at all. (Fig. 5)

Fig. 6 shows that the correlation between the growth inhibition of *P. aeruginosa* and the sum of polyphenols (R=0.7793), antioxidant activity (R=0.7026) is high, in the case of organic acids it was found moderate correlation. Whereas, the total content of anthocyanins was not effect on the inhibition of growth *P. aeruginosa*.

In Fig. 7 shows a moderate correlation between inhibition of the growth of *C. albicans* and the content of polyphenols (R=0.5120), in turn, with the sum of anthocyanins (R=0.3083), antioxidant activity (R=0.4062) was found a low dependence, and in the case of organic acids there was no correlation at all.

Conclusion

In the research, it has been determined the content of BAS, antioxidant, antimicrobial activity of the obtained extracts of *R. fruticocus* fresh fruit. The dominant content of the sum of polyphenols, anthocyanins was observed in 96% EtOH extract, whereas the organic acids was observed in aqueous extract. The 96% EtOH extract has a high level of antioxidant activity, all obtained extracts actively inhibits the growth of all studied Gram-positive, Gram-negative strains of bacteria and the fungus *C. albicans* in the range from 13 to 18 mm (diameter of growth inhibition). We have shown that there is a high correlation between the content of polyphenols, and antioxidant activity, in the case of inhibition of *B. subtillis*, whereas polyphenols and anthocyanins highly depends on antioxidant activity. These findings show the great potential in the development and creation of new medicines with antimicrobial, antioxidant effects that are not inferior to, and even superior to, the effects of synthetic analogues.

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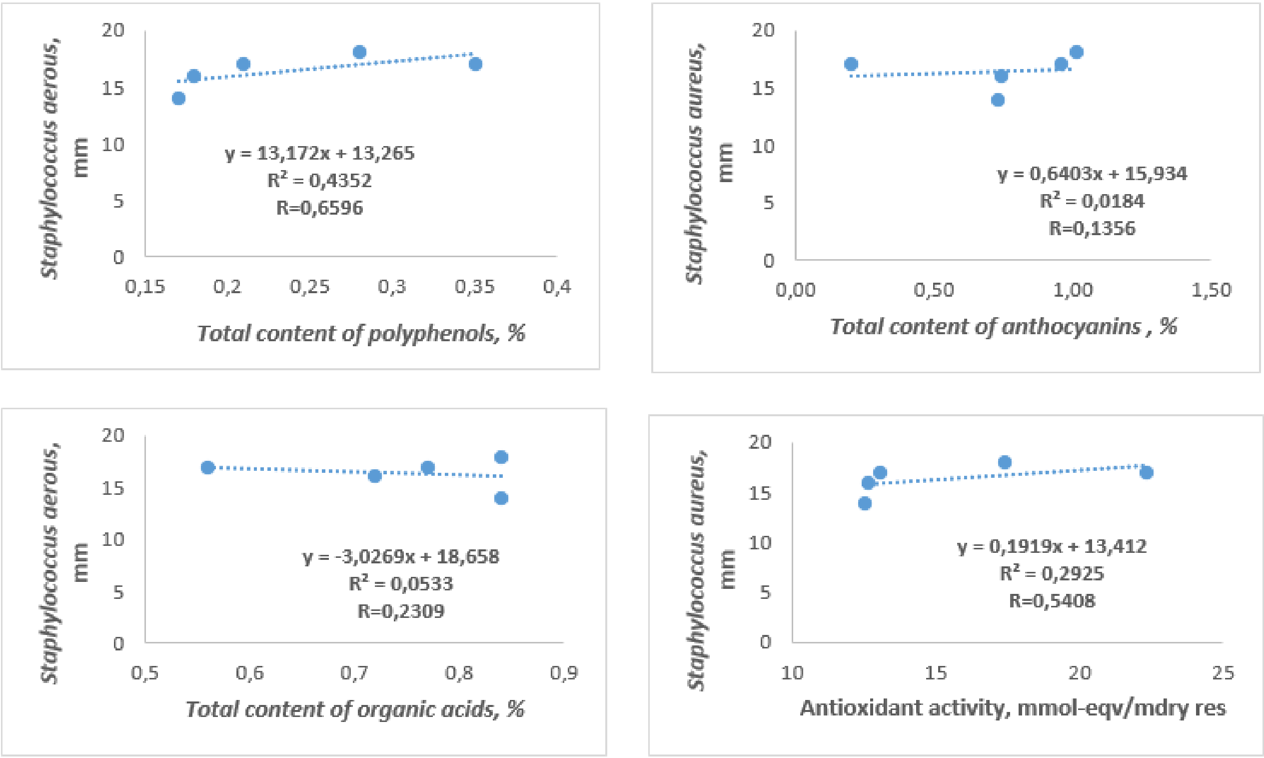

Figure 2. Correlation relationship between value of antibacterial activity against *Staphylococcus aureus* and total content of polyphenols, anthocyanins, organic acids and antioxidant activity

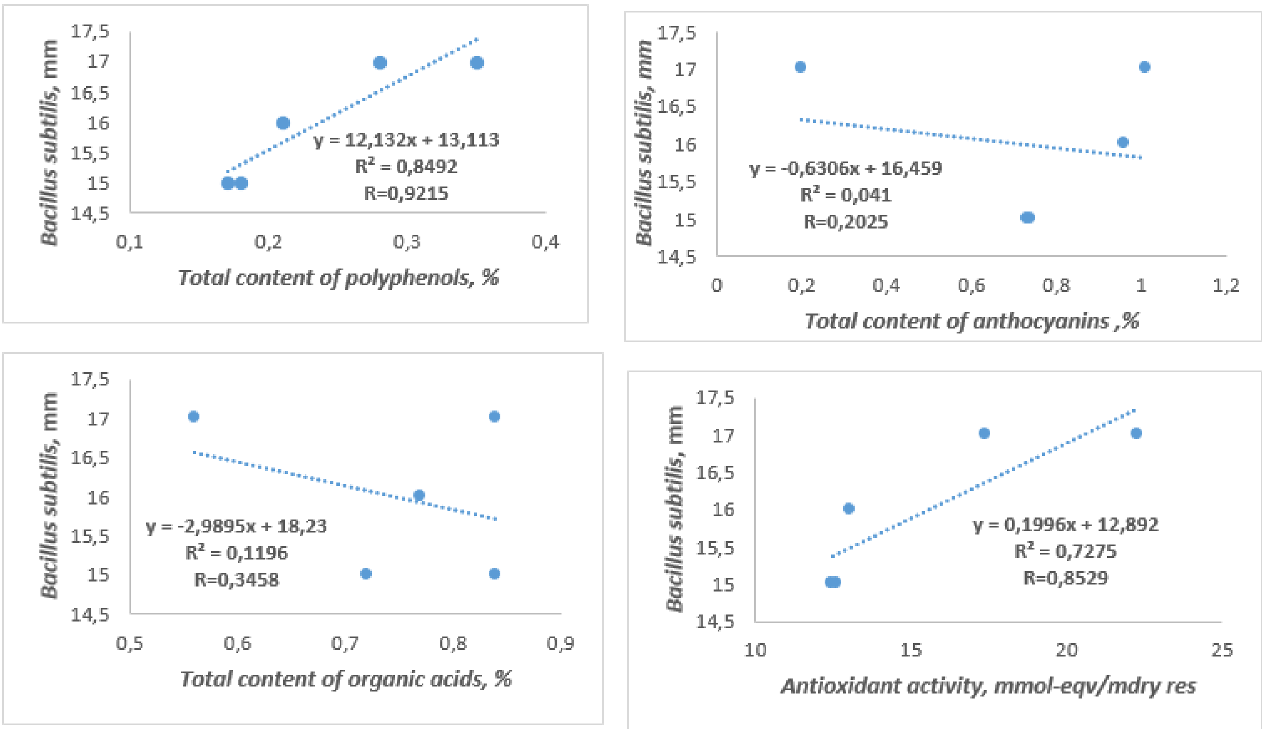

Figure 3. Correlation relationship between value of antibacterial activity against *Bacillus subtilis* and total content of polyphenols, anthocyanins, organic acids, and antioxidant activity

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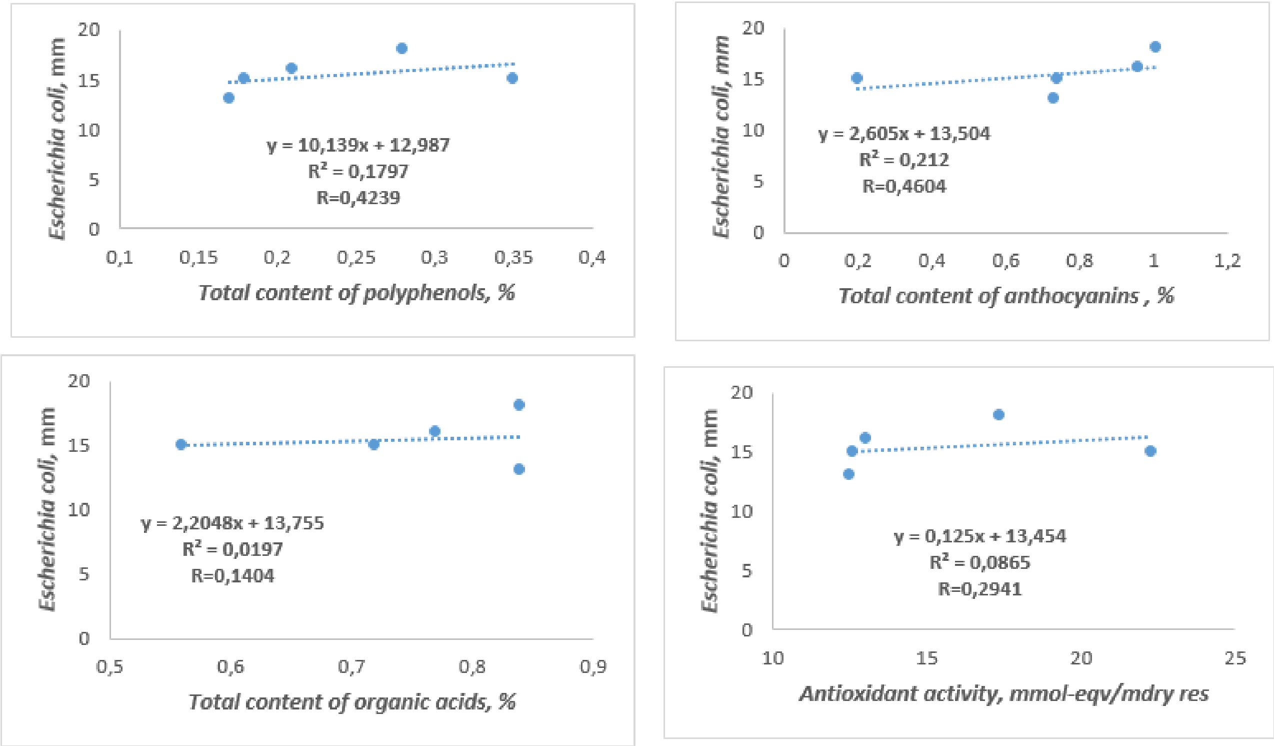

Figure 4. Correlation relationship between value of antibacterial activity against *Escherichia coli* and total content of polyphenols, anthocyanins, organic acids, and antioxidant activity

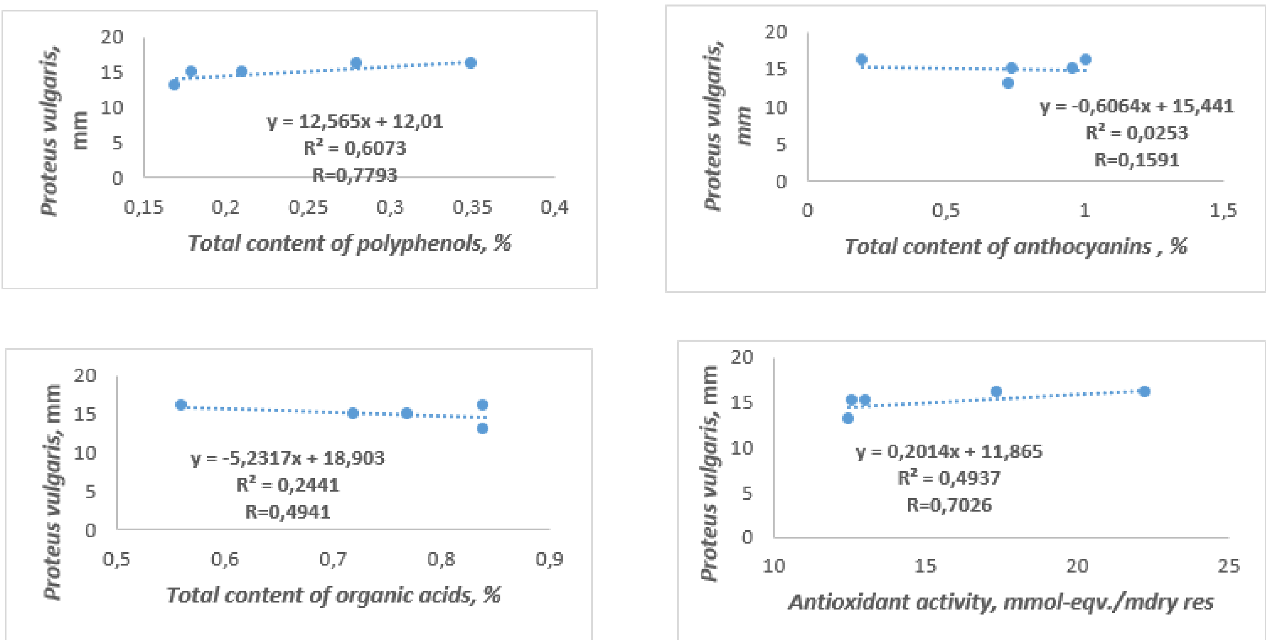

Figure 5. Correlation relationship between value of antibacterial activity against *Proteus vulgaris* and total content of polyphenols, anthocyanins, organic acids, and antioxidant activity

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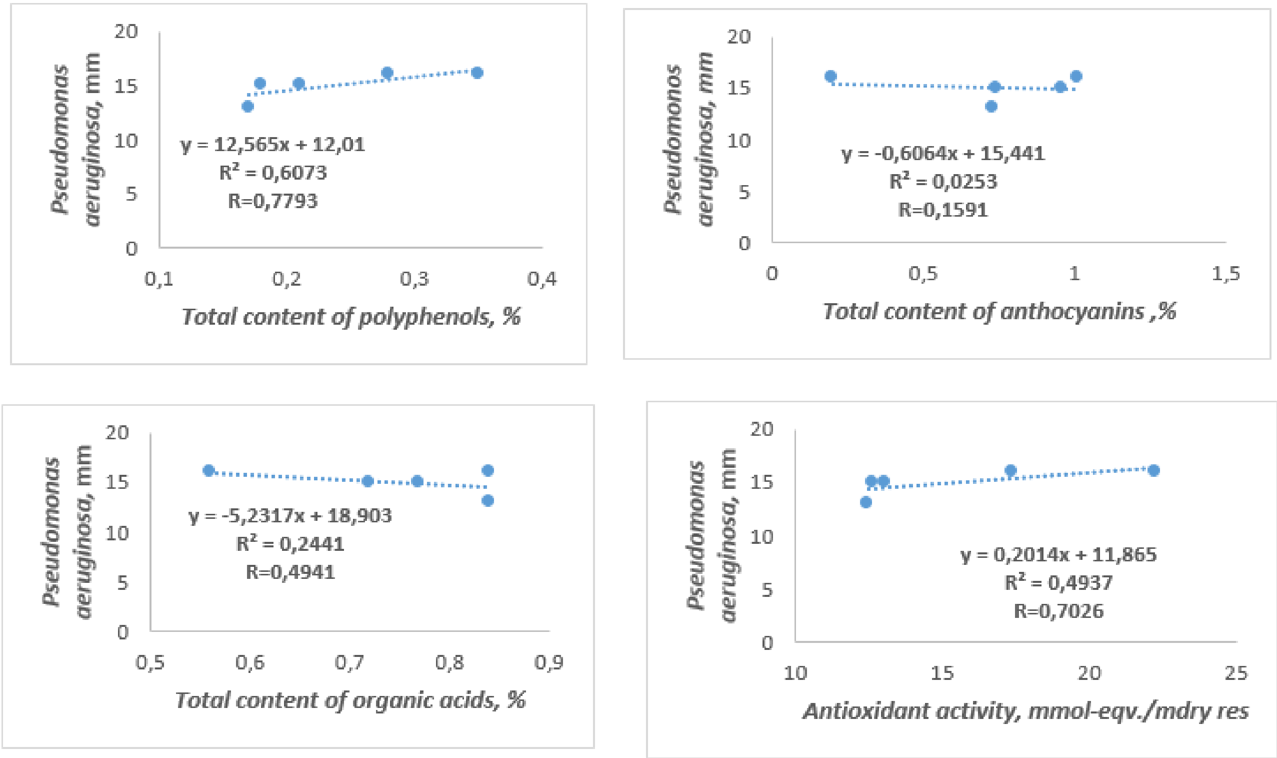

Figure 6. Correlation relationship between value of antibacterial activity against *Pseudomonas aeruginosa* and total content of polyphenols, anthocyanins, organic acids, and antioxidant activity

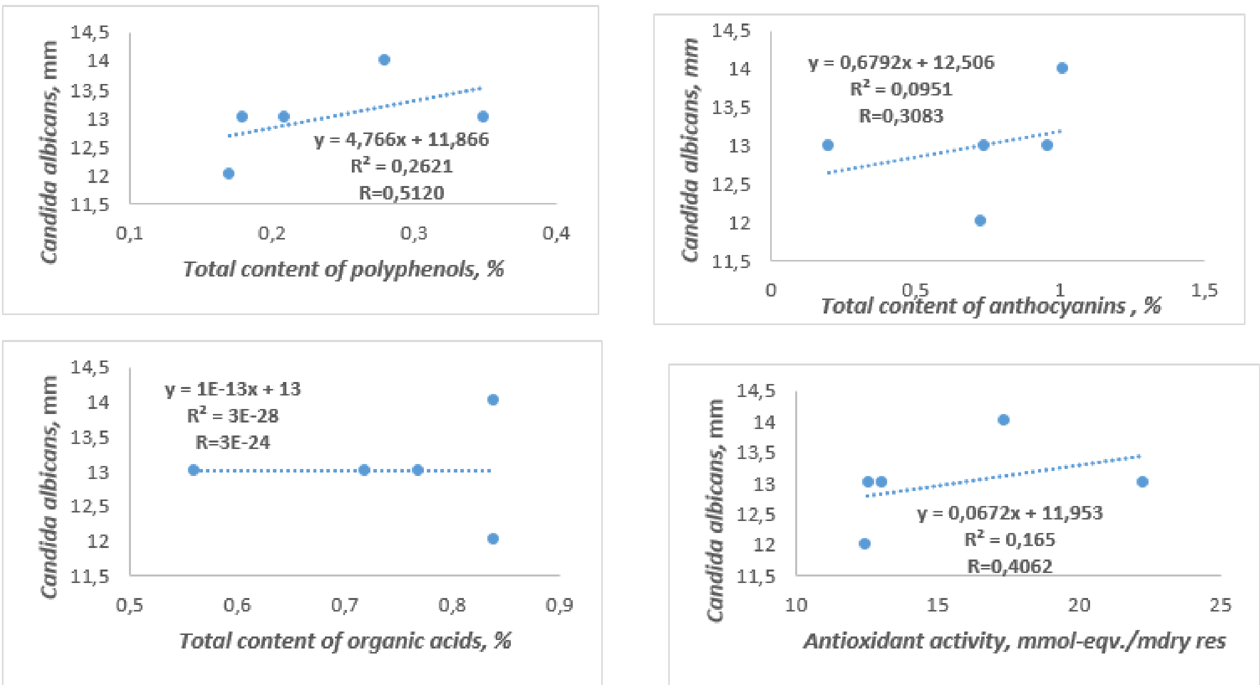

Figure 7. Correlation relationship between value of antibacterial activity against *Candida albicans* and total content of polyphenols, anthocyanins, organic acids, and antioxidant activity

Investigation relationship between antimicrobial, antioxidant activity and biologically active compounds of blackberry (*Rubus fruticocus* L.) fresh fruit liquid extracts

Artem Marchenko, Olexander Maslov, Mykola Komisarenko, Svitlana Ponomarenko, Tetyana Osolodchenko, Sergii Kolisnyk

Introduction. The search for natural antibacterial agents has gained significant interest in recent years, driven by the growing concerns over antibiotic resistance and the desire for natural alternatives. Fresh blackberries, known for their rich nutritional profile and high antioxidant content, have attracted attention for their potential antibacterial properties. Understanding the antibacterial potential of blackberries could provide insights into their use in natural medicine and food preservation. **Material and methods.** The quantity of phenolic compounds, anthocyanins was determined by spectrophotometric method of analysis, whereas organic acids by alkalimetric method; antioxidant activity of obtained extracts was evaluated by potentiometric method, antimicrobial was determined by method of "well". **Results and Discussion.** Results demonstrates the highest amount of polyphenols, anthocyanins were 0.35±0.01, 0.29±0.02 in 96% ethanolic extract, respectively. The organic acids were dominated in aqueous and 60% EtOH extracts (0.84±0.02%). The most potent antioxidant property possessed 96% EtOH extract of blackberry fresh fruit. There is a high correlation between the content of polyphenols, antioxidant activity and inhibition of *Bacillus subtillis*, whereas antioxidant power highly depends on total polyphenols and anthocyanins. **Conclusion**. These findings show the great potential of blackberry extracts in the development and creation of new medicines with antimicrobial, antioxidant effects that are not inferior to the action of synthetic analogues.

Key words*: anthocyanins, phenolic compounds, organic acid, correlation analysis, blackberry, fresh fruit*

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