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ACTION OF AQUEOUS EXTRACTS OF BEARBERRY AND COWBERRY LEAVES AND WILD CAMOMILE AND PINEAPPLE-WEED FLOWERS ON *ESCHERICHIA COLI* SURFACE STRUCTURES

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ABSTRACT

The action of aqueous extracts of bearberry and cowberry leaves and wild camomile and pineapple-weed flowers on the aggregation activity of Escherichia coli *strains was studied by way of salt aggregation test (SAT). We established the titers at which the aqueous extracts of bearberry and cowberry were able to enhance the aggregation of microbes and the titers at which the aqueous extracts of wild camomile and pineapple-weed were able to block it. The action of bearberry and cowberry aqueous extracts on the surface structures of* E. coli *depended on the methods used for preparing the extracts. The titers of bearberry and cowberry maceration were 4–8-times higher than those of the corresponding decoctions. After heating the maceration of the above mentioned drugs, the titers fell 64- and 256-times, respectively. Aqueous extracts from bearberry and cowberry contain two types of substances enhancing the aggregation of* E. coli*; the substances are thermostable in decoctions and thermolabile in macerations. The constituents of wild camomile and pineapple-weed flowers blocking the aggregation of* E. coli *are thermostable.*

INTRODUCTION

Bearberry, cowberry, wild camomile and pineapple weed are among the widely spread and most frequently used medicinal herbs in the Baltic countries. In traditional medicine they are mainly used in the treatment of various infectious inflammatory processes and their mechanism of action, apart from being antiflogistic and antispasmodic, is attributed to their antimicrobial properties. However, on the basis of relevant studies (Ahn et al., 1994) and our earlier investigations (Koppel et al., 1993), it has become evident that the antimicrobial activity of these medicinal herbs, when introduced into the organism, is too low to kill microbes or inhibit their growth. Hence, the mechanism of action of those herbs must be based on some other mechanisms.

In our previous studies we have seen that a short exposure to aqueous extracts of some medicinal herbs such as bearberry, cowberry and Saint John's wort enhance, whereas those of other herbs such as wild camomile, pineapple weed, marigold, milfoil and peppermint, attenuate aggregation (i.e., sticking of microbial cells to each other and formation of conglomerates visible with the naked eye) of *E. coli* strains (Türi & Türi, 1995). The aggregativity of microbes correlates directly with their surface structures (Lindhal et al., 1981, Rozgonyi et al., 1990) which, in turn, correlate with the hydrophobicity of microbes (Rozgonyi et al., 1985). The higher the hydrophobicity of microbial cells, the higher their adhesion activity, i.e., the ability to bind the receptors of a macroorganism (Andreoni, 1994). Adhesion activity has been shown to be in correlation with the virulence of microbial strains (Law, 1994).

The aim of the present study was to compare the action of aqueous extracts from leaves of bearberry and cowberry and from flowers of wild camomile and pineapple-weed, obtained by different techniques, to the aggregation activity of *E. coli* strains, as well as to study some properties of the substances capable of influencing such activity.

Keywords: Arctostaphylos uva-ursi, Vaccinium vitis-idaea, Matricaria recutita, Matricaria matricarioides, aqueous extracts, *Escherichia coli*, hydrophobicity, Wild camomile, Pineapple-weed, Bearberry, Cowberry.

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MATERIALS AND METHODS

Plant Materials

The plant materials were collected in Estonia in the year 1996. Medicinal plants more widely used in the traditional medicine of the Baltic countries were selected for the study. Wild camomile [*Matricaria recutita* L. Asteraceae] was grown at the experimental station of the Department of Pharmacy, University of Tartu. The leaves of bearberry [*Arctostophylos uva-ursi* (L.) Spreng. Ericaceae] and cowberry [*Vaccinium vitis-idaea* L. Ericaceae] and the flowers of pineapple-weed [*Matricaria matricarioides* (Less.) Port Asteraceae] were collected in Tartu county and identified at the Department of Pharmacy, University of Tartu. The quality of all these medicinal herbs met the requirements of the pharmacopoeia (Maškovski et al., 1990; European Pharmacopoeia, 1995).

Preparation of Aqueous Extracts

Preparation of infusion and decoction. For the study, aqueous extracts of medicinal herbs were prepared in the proportion 1:10. Ground drug (10 g) was placed into an infuser and distilled water was poured over the drug. The amount of water was calculated according to the drug absorption coefficient (1.4 for bearberry leaves; 2.0 for cowberry leaves; 3.4 for wild camomile; 2.0 for pineapple-weed). Infusions were prepared from the camomile and pineapple-weed flowers (infusion time at 100°C 15 min, cooling time 45 min). Decoctions were prepared from bearberry and cowberry leaves (infusion time at 100°C 30 min); filtering was performed while the decoctions were still hot. The infusions and decoctions were filtered through a cotton wad. After filtering, water was added until the desired amount was reached (Maškovski et al., 1990).

Preparation of maceration. For the preparation of two-fold maceration, 20 g of ground plant material was treated with 120 ml of distilled water, mixed and left to stand for 4 days in a refrigerator (at 4°C) for maceration. From time to time the contents were shaken. The obtained liquid was separated by compressing. Again, 100 ml of distilled water was added to remainder of the drug, left to stand for maceration for 3 days at 4°C, with periodic shaking. The liquid was separated by compressing and added to the previously obtained liquid, resulting in cold maceration, which was divided into two equal parts. Heated maceration was prepared by heating one part of cold maceration at 100°C for 30 min.

Analysis of Aqueous Extracts

In aqueous extracts, the amount of extractive substances dissolved in water and the content of tannins were determined. In addition, we determined the content of arbutin in aqueous extracts from bearberry and cowberry.

Determination of Extractive Substances

For the determination of extractive substances, approximately 5 g (weighed with a precision of 0.0001 g) of aqueous extract was evaporated in a glass utensil with a constant mass. The remainder was heated in a drying chamber at 100–105°C for 1 h, cooled in an exsiccator for 30 min and weighed. Drying and weighing were repeated until the difference between two successive measurments did not exceed 0.0005 g. The content of extractive substances was calculated in percentages (w/w).

Determination of Tannins

For the determination of tannins, 500 ml of water and 25 ml of indigocarmin solution (1 g indigocarmin was mixed with 25 ml of concentrated sulphuric acid to which an additional 25 ml of concentrated sulphuric acid was added and diluted with water to 1000 ml) were added to 5 ml of aqueous extract (aqueous extract of bearberry and cowberry were diluted with water 1:25) and titrated with 0.02 N potassium permanganate until a greenish-yellow color appeared. Simultaneously, a 25 ml solution of indigocarmin in 500 ml water was titrated with 0.02 N potassium permanganate.

One ml of 0.02 N potassium permanganate corresponds to 0.8314 mg of tannin. The content of tannin was calculated in percentages (w/w) (Maškovski et al., 1987).

Determination of Arbutin

Four ml of decoction was placed into a 250 ml volumetric flask and filled with water up to the mark. Five ml of the solution was introduced into a separating funnel, and 45 ml of water, 1.0 ml of 2% (w/) solution of aminopyrazolone, 0.5 ml of dilute ammonia and 1.0 ml of 8.0% (m/) solution of potassium ferricyanide were added successively, mixing after each addition. The solution was allowed to stand for 5 min and shaken with 25 ml of methylene chloride. The methylene chloride layer was filtered through a plug of absorbent cotton, soaked in methylene chloride, into a 100 ml volumetric flask. The aqueous layer was again shaken with three quantities, each 25 ml, of methylene chloride; the combined methylene chloride layers were diluted to 100 ml

with the same solvent. The absorbance of the solution was measured at 455 nm (specific absorbance of anhydrous arbutin, 648) using water as a compensation liquid. The content of arbutin was calculated in percentages (w/w) (European Pharmacopoeia, 1995).

Bacterial Strains

Strains of *E. coli* were selected as test microbes. This microbe is widespread among humans and animals, and its potentially pathogenic (opportunic) strains cause infections of very different types and localisations such as uroinfections and some inflammatory processes. The cultures of *E. coli* were isolated from a single colony grown on a McConkey agar plate and indentified by conventional tube biochemical tests for *Enterobacteriaceae* (Farmer & Kelly, 1991). On the basis of preliminary experiments, two strains of *E. coli* were selected for the study: one hydrophobic strain A-17 of average activity and one non-hydrophobic strain KU-14. The cultures of *E. coli* were grown on an agar slant at 37°C for 18–20 h. The microbial cells obtained from slant agar were suspended in 0.01 M potassium phosphate buffer (pH 6.8) according to the McFarland optical density standard to a final concentration of 3×10^9 microbial cells/ml.

Determination of the activity of microbial surface structures

For the determination of the activity of microbial surface structures, the salt aggregation test (SAT) according to Ljungh et al. (1985) was used. The essence of the test is based on the phenomenon that at certain concentrations of ammonium sulphate, hydrophobic microbial strains aggregate into conglomerates that are easily detectable under a light microscope.

To affect the aggregation activity of *E. coli*, 0.8 ml of microbial suspension (3×10^9 microbes/ml) was mixed with 0.8 ml of an aqueous extract (or with a dilution 1:2, 1:4, 1:8, etc., made of an aqueous extract) and left to stand at room temperature for 15 min (mixture I). Ammonium sulphate solution (0.2 ml of 0.05, 0.5, 1.0, 1.5 and 3.0 M, respectively) in phosphate buffer (pH 6.8) was introduced into wells of a Nunclon R plate, and 0.2 ml of mixture I was added. The plate was shaken slowly for 5 min and microbial aggregation was established visually under a microscope using a magnification of 12.5×. The test was considered positive or negative according to the presence or absence of aggregation after 5 min.

A separate control experiment was carried out in which microbial suspension was not affected by an aqueous extract or its dilutions; 0.8 ml of microbial suspension was mixed with 0.8 ml of phosphate buffer (mixture II); the subsequent procedure was carried out as described above.

Using this test, the highest dilution (titer) of an aqueous extract capable of affecting aggregativity of microbes was determined; it also reflects the activity of the aqueous extract. On the basis of both the determined titers and the results obtained from the analysis of aqueous extracts, minimal amounts of constituents capable of affecting surface structures of microbes were calculated.

RESULTS

The content of extractive substances in the decoction and maceration of bearberry was approximately the same (3.85 and 3.84%, respectively) (Table 1). Arbutin constituted 19.8–23.6% and tannins 46.4–49.9% of all extractive substances in aqueous extracts of bearberry. The content of extractive substances in the decoction and maceration of cowberry was approximately the same as well (3.02 and 3.00%, respectively). Among extractive substances in the aqueous extract of cowberry, arbutin constituted 20.3% and tannins 23.7–24.5%.

The infusion of wild camomile contained 1.8% and maceration 2.4% of extractive substances. Tannins constituted 2.0% of extractive substances in infusion and 5.5% in maceration. The infusion of pineapple-weed contained 2.0% and maceration 2.4% of extractive substances. Tannins constituted 6.0% of extractive substances in infusion and 1.7% in maceration.

The highest dilutions (titers) of aqueous extracts from bearberry leaves that enhanced the aggregativity of the hydrophobic A-17 strain of *E. coli* were 1:128 for decoction, 1:1024 for cold maceration, and 1:4 for heated maceration (Table 2). The minimal amounts of extractive substances affecting surface structures of the microbe were 240.6, 30 and 7680.0 μg, respectively. The titers of aqueous extracts from cowberry leaves having the same effect were 1:64, 1:256 and 1:4, and the amounts of extractive substances 377.5, 93.8 and 6000.0 μg, respectively. Aqueous extracts from bearberry changed the *E. coli* non-hydrophobic KU-14 strain into a hydrophobic strain at dilutions 1:64, 1:256 and 1:4 (Table 3); the respective amounts of extractive substances were 481.3, 120.0 and 7680.0 μg. The titers of aqueous extracts of cowberry having the same effect were 1:64, 1:256 and 1:4, the amount of extractive substances being 377.5, 93.8 and 6000.0 μg, respectively.

Table 1. Constituents of aqueous extracts (%).

Constituents	Bearberry		Cowberry	
	Decoction	Maceration	Decoction	Maceration
Extractive substances of these:	3.85 (100.0)	3.84 (100.0)	3.02 (100.0)	3.00 (100.0)
arbutin	0.91 (23.6)	0.76 (19.8)	0.74 (24.5)	0.61 (20.3)
tannins	1.92 (49.9)	1.78 (46.4)	0.74 (24.5)	0.71 (23.7)
other substances	1.02 (26.5)	1.30 (33.8)	1.54 (51.0)	1.68 (56.0)
Constituents	Wild camomile		Pineapple-weed	
	Infusion	Maceration	Infusion	Maceration
Extractive substances of these:	1.82 (100.0)	2.44 (100.0)	2.01 (100.0)	2.36 (100.0)
tannins	0.10 (5.5)	0.05 (2.0)	0.12 (6.0)	0.04 (1.7)
other substances	1.72 (94.5)	2.39 (98.0)	1.89 (94.0)	2.32 (98.3)

Table 2. Titers of aqueous extracts from bearberry and cowberry leaves affecting the activity of surface structures of the hydrophobic strain of *E. coli* and their relation to constituents[a].

Titer and constituents μg	Bearberry			Cowberry		
		Maceration			Maceration	
	Decoction	cold	heated	Decoction	cold	heated
Titer	1:128	1:1024	1:4	1:64	1:256	1:4
Extractive substances of these:	240.6	30.0	7680.0	377.5	93.8	6000.0
arbutin	56.9	5.9	1520.0	92.5	19.1	1220.0
tannins	120.0	13.9	3560.0	92.5	22.2	1420.0
other substances	63.7	10.2	2600.0	192.5	52.5	3360.0

[a]minimal amount of extractive substances and their components calculated on the basis of titers of aqueous extracts.

Infusion, maceration as well as heated maceration from wild camomile blocked the aggregation of the *E. coli* hydrophobic A-17 strain at the same dilution, 1:16 (Table 4). The amount of extractive substances in these aqueous extracts was 910.0 and 1220.0 μg, respectively. Infusion from pineapple-weed blocked the aggregation activity of test microbes at the dilution 1:16, while maceration and heated maceration blocked it at the dilution 1:8.

DISCUSSION

From the results of this study it became evident that the enhancing action of the aqueous extracts of bearberry and cowberry leaves on the aggregation activity of *E. coli* depended to a great extent on the method by which the extracts were made. The titers of cold macerations made of bearberry and cowberry leaves were 8- and 4-times higher as compared to those of decoctions. After heating (30 min at 100°C) the titer of macerations fell 64-256 times. This indicates that the substance or substances in macerations enhancing the aggregativity of *E. coli* are thermolabile and inactive at 100°C.

We also studied if the aggregation of microorganisms was related to some extractable substances. Therefore, we determined the total amount of extractive substances in the aqueous extracts of all four herbs. Separately, we determined the amount of tannins as well as the content of arbutin in case of bearberry and cowberry.

The leaves of bearberry and cowberry contain tannin, phenolglycoside arbutin and a number of other substances. The leaves of bearberry contain gallotannin (Muravjeva, 1991; Steinegger & Hänsel, 1992) and the leaves of cowberry, catechin-type tannins (Petkov, 1988). The pharmacological activity of these herbs is attributed to tannin and arbutin (Muravjeva, 1991; Wichtl, 1994). In the organism, arbutine is hydrolyzed into glucose and hydroquinone which has some antimicrobial activity (Wichtl, 1994).

On the basis of titers of aqueous extracts from herbs affecting the aggregativity of *E. coli*, we calculated the

Table 3. Titers of aqueous extracts from bearberry and cowberry leaves affecting the activity of surface structures of the non-hydrophobic strain of *E. coli* and their relation to constituents[a].

Titer and constituents μg	Bearberry			Cowberry		
		Maceration			Maceration	
	Decoction	cold	heated	Decoction	cold	heated
Titer	1:64	1:256	1:4	1:64	1:256	1:4
Extractive substances	481.3	120.0	7680.0	377.5	93.8	6000.0
of these:						
arbutin	113.8	23.8	1520.0	92.5	19.1	1220.0
tannins	240.0	55.6	3560.0	92.5	22.2	1420.0
other substances	127.5	40.6	2600.0	192.5	52.5	3360.0

[a]minimal amount of extractive substances and their components calculated on the basis of titers of aqueous extracts.

Table 4. Titers of aqueous extracts of wild camomile and pineapple-weed affecting the activity of surface structures of the hydrophobic strain of *E. coli* and their relation to constituents[a].

Titer and constituents μg	Wild camomile			Pineapple-weed		
		Maceration			Maceration	
	Decoction	cold	heated	Decoction	cold	heated
Titer	1:16	1:16	1:16	1:16	1:8	1:8
Extractive substances	910.0	1220.0	1220.0	1005.0	2360.0	2360.0
of these:						
tannins	50.0	25.0	25.0	60.0	40.0	40.0
other substances	860.0	1195.0	1195.0	945.0	2320.0	2320.0

[a]minimal amount of extractive substances and their components calculated on the basis of titers of aqueous extracts.

minimal amount of extractive substances in aqueous extracts which were capable of changing the aggregativity of test microbes. In this respect, the most significant differences were established when the activity of extractive substances from decoctions and from cold and heated macerations from the leaves of bearberry and cowberry were compared. A comparison of cold maceration and decoction from bearberry showed aggregation of the hydrophobic strain of *E.coli* with 8- to 10-fold higher amounts of extractive substances in the latter case. For the non-hydrophobic strain of *E. coli*, the differences in the amount of these substances between cold maceration and decoctions were smaller (3–5-fold). When comparing the activity of extractive substances in cold maceration and decoction made from the leaves of cowberry, differences were relatively small and similar in both *E. coli* strains.

Even greater changes in the activity of extractive substances appeared after heating macerations in order to achieve aggregation of the *E. coli* hydrophobic strain. The heated maceration of bearberry leaves had to contain 256-times more extractive substances, arbutin, tannin and other substances than cold maceration. In experiments with the non-hydrophobic strain, these differences were smaller but still quite considerable (64-fold). Similar large differences in the activity of extractive substances were revealed in experiments with hydrophobic and non-hydrophobic strains of *E. coli* when cold and heated macerations made from cowberry leaves were compared.

The high activity of extractive substances was most evident in experiments with cold maceration from bearberry leaves. Extractive substances (30 μg) were sufficient to produce aggregation of the hydrophobic strain *E. coli*. To achieve the same phenomenon with the non-hydrophobic strain of *E. coli*, maceration had to contain 120 μg of extractive substances, i.e., four times more than in the case of the hydrophobic strain. This confirms our suggestion that the phenomenon of aggregation of *E. coli* cells, caused by extractive substances, is related to the activation of surface structures. Although cold macerations from both bearberry and cowberry leaves activate surface structures of *E. coli*, significant differences were detected in their

activity. To induce aggregation of the hydrophobic strain of *E. coli*, 3-times more extractive substances from cowberry were needed (93.8 μg) as compared to those from bearberry. It is also worth mentioning that the activity of cold maceration from cowberry leaves was similar for both hydrophobic and non-hydrophobic strains of *E. coli*.

These results allow us to conclude that leaves of bearberry and cowberry contain at least two types of substances or groups of substances which are capable of enhancing the activity of surface structures of *E. coli* and inducing aggregation of microbial cells. One of these is thermostable and can be extracted from drugs with hot water, i.e., by preparing decoctions. The other substance or substances, having the same biological activity, are thermolabile, significantly more active, and can be extracted relatively easily with cold water.

Contrary to the action of aqueous extracts from bearberry and cowberry, those from wild camomile and pineapple-weed blocked the aggregativity of the hydrophobic strain of *E. coli*. As the blocking activity of infusions as well as cold and heated macerations was almost the same, it can be concluded that these substances are thermostable.

Flowers of wild camomile contain lipophilic (components of ethereal oil, coumarins, phytosterins, wax-like substances, flavonglucosides), hydrophilic (flavonoids, mucilage, cholin, phenylcarboxy acids, amino acids) and other constituents (Wichtl, 1994, Ammon and Kaul, 1992). There are also indications of the presence of tannins (Duke, 1992). Flowers of pineapple-weed contain a number of the same substances as flowers of wild camomile (Arak and Raal, 1987; Arak et al., 1988).

This study demonstrated that (1) aqueous extracts from bearberry and cowberry contain substances which enhance the aggregativity of *E. coli*, and (2) wild camomile and pineapple-weed aqueous extracts contain substances which block this activity.

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