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Study on the activity of *Rubus caesius* L. extracts against MRSA

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INTRODUCTION

In one of its reports, WHO published a list of pathogenic bacteria that pose the greatest threat to human health due to the rapidly growing resistance to currently used antibiotics. This group is called "ESKAPE" and includes among others, Gram-positive resistant strains of *Staphylococcus aureus*. This bacteria can cause a range of infections, from folliculitis and abscesses to severe cases like sepsis and approximately 15% of invasive infections in hospitals worldwide. Methicillin-resistant *S. aureus* - MRSA in addition to resistance to β-lactam antibiotics, is resistant to aminoglycosides, fluoroquinolones, macrolides, chloramphenicol, and tetracycline. Some of those strains can produce a biofilm. The growing resistance of bacteria to available antibiotics forces the search for alternative antibacterial drugs. Plants of the genus *Rubus* are a source of natural compounds used in many infectious diseases. *Rubus caesius* (dewberry) contains among others: anthocyanins, tannins, flavonoids, and phenolic acids known for their antioxidant and antibacterial properties [1].

RESULTS & DISCUSSION

The antibacterial activity of two European dewberry leaf extracts (L_{H2O}, L_{EtOH}) were tested by the broth microdilution method against 3 reference bacterial strains, *S. aureus* ATCC 6538, *S. epidermidis* ATCC14990, *S. aureus* ATCC43300 MRSA and two clinical strains. The obtained results showed that the most active extract was L_{H2O}, demonstrated the MIC (minimum bacteriostatic concentration) values of 0.16 mg/mL against reference strains of *S. aureus* and MIC of 0.39 mg/mL and 0.78 mg/mL against clinical strains. The L_{EtOH} extract showed slightly higher MIC values against reference strains of *S. aureus* than the L_{H2O} extract, but was active against *S. epidermidis* (MIC 0.625 mg/mL). L_{EtOH} extract showed inhibition at similar concentrations as L_{H20} against clinical strains. Both extracts showed similar bactericidal activity (MBC, minimum bactericidal concentration) in the range of concentrations 3.125 – 12.5 mg/mL.

Table. Minimum inhibitory concentrations (MIC) [mg/mL] and minimum bactericidal concentrations [mg/mL] of *R. caesius* extracts and gramicidin on reference bacterial strains

Bacteria	Gramicidin		Extracts [mg/mL]			
			L_{EtOH}		L_{H2O}	
	MIC	MBC	MIC	MBC	MIC	MBC
S. aureus ATCC 6538	0.03125	>0.125	0.16	10	0.16	5
S. epidermidis ATCC14990,	0.00196	0.125	0.625	5	10	10
S. aureus ATCC43300 MRSA	0.125	>0.125	0.625	5	0.16	5
MRSA 12673	0.03125	>0.125	0.78	12.5	0.39	3.125
MRSA 15732	0.06250	0.125	0.78	6.25	0.78	12.5

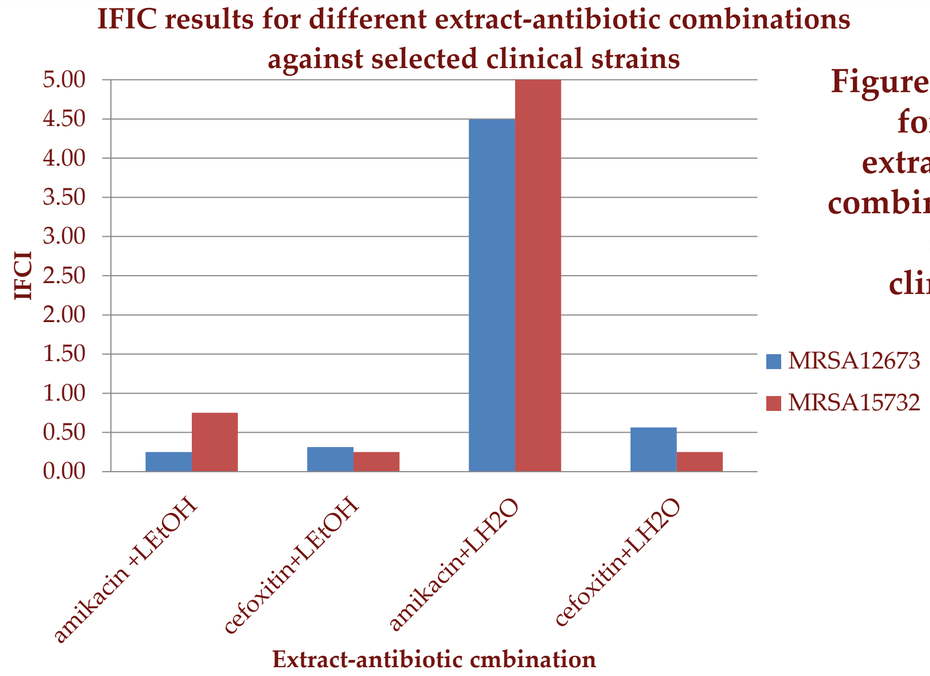

Figure 1. FICI results for different extract-antibiotic combinations against selected clinical strains

Using the checkerboard assay method for planktonic bacteria, we determined the Fractional Inhibitory Concentration Index (FICI) of L_{H2O} and L_{EtOH} extracts in combination with amikacin and cefoxitin. The results are presented in a Figure 1. The obtained FICI values below 0.5 indicate synergy of the extract with the antibiotic, values 1 < FICI < 4 indicate an additive effect and FICI > 4 correspond to antagonism. In our studies, amikacin + L_{EtOH} against the MRSA12673 strain, cefoxitine + L_{EtOH}, against both tested strains, and cefoxitine + L_{H2O} against MRSA15732 showed synergy. Whereas, antagonism against both tested strains was demonstrated in case of combination of amikacin + L_{H2O}.

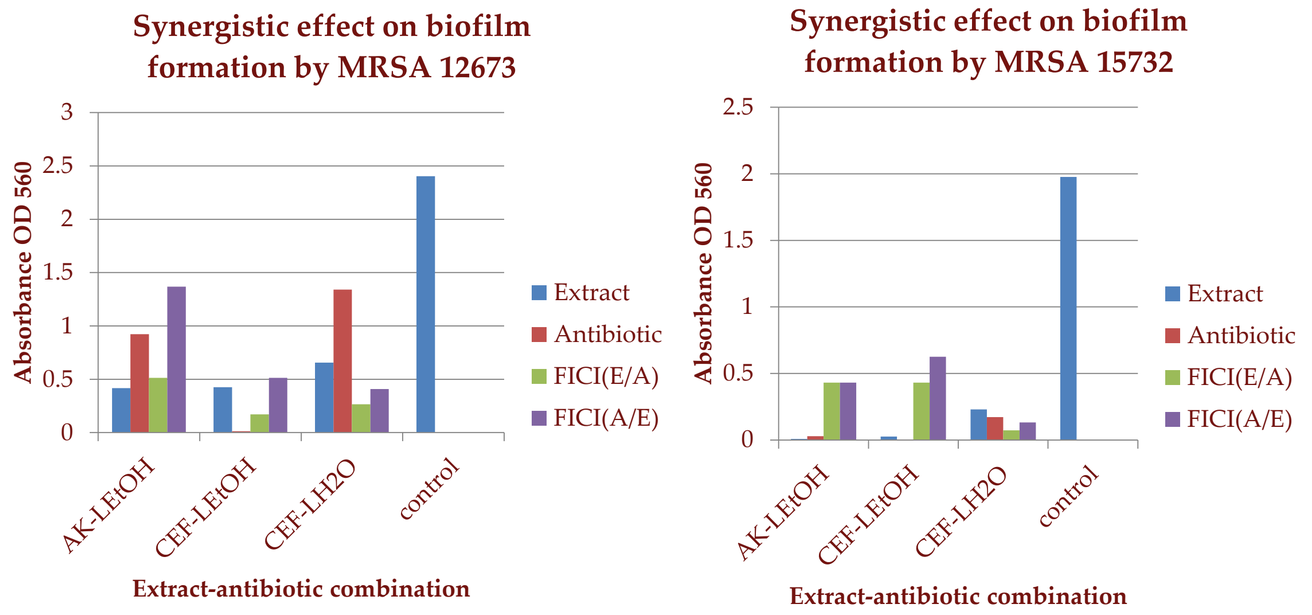

Figure 2. Synergistic effect of combinations - antibiotics and *R. caesius* extract son biofilm formation by MRSA strains

AK- Amikacin, CEF – cefoxitin, Extract – the inhibitory concentration of Extract alone (FICI) Antibiotics – the inhibitory concentration of Antibiotic alone (FICI)FICI (E/A) – the inhibitory concentration of Extract in combination with Antibiotic (acording to FICI values <0.5) ;FICI (A/ E) – the inhibitory concentration of Antibiotic in combination with Extract (acording to FICI values <0.5)

Among the concentrations tested, (Figure 2) only the combination of cefoxitin with L_{H2O} extract showed higher activity in inhibition biofilm formation by both MRSA strains used in the study than the of the compounds alone. It can be assumed that this combinatin effectively affects quorum sensing of bacteria and thus contributes to disturbances in biofilm formation.

We suggest, that our results will influence the reduction of antibiotic doses and increase their therapeutic effect, which may potentially lead to faster elimination of microorganisms from the human body.

REFERENCES

[1] Hering, A.; et al. Polyphenolic Characterization, Antioxidant, Antihyaluronidase and Antimicrobial Activity of Young Leaves and Stem Extracts from *Rubus caesius* L. **Molecules** 2022, 27, 6181. https://doi.org/10.3390/molecules27196181