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Antibacterial properties of thalloid liverworts *Marchantia polymorpha* L., *Conocephalum conicum* (L.) Dum. and *Pellia endiviifolia* (Dicks.) Dumort

IVANA M. IVKOVIĆ[1], DANKA R. BUKVIČKI[1]*, MIROSLAV M. NOVAKOVIĆ[2], STEFAN G. IVANOVIĆ[2], OLJA J. STANOJEVIĆ[1], IVAN C. NIKOLIĆ[1] and MILAN M. VELJIĆ[1]

[1]*University of Belgrade , Faculty of Biology, Institute of Botany and Botanical Garden "Jevremovac", Takovska 43, 11000 Begrade, Serbia and* [2]*University of Belgrade – Institute of Chemistry, Technology and Metallurgy, Department of Chemistry, Njegoševa 12, 11000 Belgrade, Serbia*

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Abstract: The antimicrobial activity of methanol extracts of three thalloid liverworts, *Marchantia polymorpha*, *Conocephalum conicum* and *Pellia endiviifolia* and bis-bibenzyl marchantin A, the most dominant compound in the methanol extract of *M. polymorpha*, have been investigated in this research. ^{1}H-NMR spectroscopy revealed that the *M. polymorpha* and *P. endiviifolia* extracts of liverwort contain terpenes, oils, sugars and bis-bibenzyls, while these specific macrocyclic compounds were absent in the *C. conicum* extract. The antimicrobial potential was tested on eight bacterial strains. Antimicrobial effects of extracts and marchantin A were observed against Gram-positive bacteria, while they showed no effect against Gram-negative bacteria in both methods used – well diffusion and broth microdilution.

Keywords: bis-bibenzyls; marchantin A; extracts; antimicrobial activity; ^{1}H-NMR.

INTRODUCTION

Liverworts are small, slow-growing, terrestrial plants with cosmopolitan distribution and are mostly found in high-humidity habitats. Liverworts can be divided into two types – leafy and thalloid.

With a few exceptions among the vascular plants, liverworts are the only plants that contain specific cellular organelles, oil bodies.[1] Since the oil bodies vary in size, shape, color, number, and distribution, they are important biological markers.[2] These organelles are the sites of the synthesis of different lipophilic mono-, di- and sesquiterpenes and aromatic compounds (bibenzyls, bis-benzyls, benzoates, cinna-

* Corresponding author. E-mail dankabukvicki@gmail.com
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mates, naphthalenes, isocoumarins). Some liverworts emit a specific smell and have an intense bitter taste with the role in repelling herbivores and insects. They are resistant to bacteria and micromycetes, and show plant protection against UV radiation.[3]

Secondary metabolites derived from liverworts, especially terpenoids and aromatic compounds, showed diverse biological activities – antibacterial, antifungal and antioxidant, cytotoxic and anti-HIV-1, and they are known as enzyme inhibitors, as well as cardiotonic and vasopressin antagonists.[3]

Resistance of microorganisms to synthetic antibiotics is increasing. This problem has led to increased interest in natural products of plant origin as an alternative in the fight against bacterial infections. Research in the last two decades has led to the discovery of a large number of natural products showing a wide range of activities against various pathogens.[4]

The main types of chemical compounds and the antimicrobial activity of three thalloid liverwort extracts, *Marchantia polymorpha*, *Conocephalum conicum* and *Pellia endiviifolia*, were examined in this study.

EXPERIMENTAL

Plant materials

Marchantia polymorpha L. was collected at the Kopaonik Mountain, *Conocephalum conicum* (L.) Dum. at Petnica cave, *Pellia endiviifolia* (Dicks.) Dumort. at Bajina Bašta, all localities in Serbia, and identified by M. V., Faculty of Biology, Institute of Botany and Botanical Garden "Jevremovac", University of Belgrade, Serbia. Voucher specimens of these species, No.17504, No.17762 and No.17503, respectively, are deposited in the Herbarium of the Institute of Botany and Botanical Garden "Jevremovac", University of Belgrade (BEOU). The collected material was air-dried, then packed in paper bags and stored in a dry and dark place at room temperature until further use. Marchantin A was kindly obtained from Yoshinori Asakawa who worked on *M. polymorpha* for almost 50 years and collected a large amount of this compound[5] and its purity was checked by ^{1}H-NMR.

Bacterial strains and growth conditions

Examination of the antibacterial activity of liverworts' extracts was conducted on four Gram-positive, *Staphylococcus aureus* (ATCC 25923), *Listeria monocytogenes* (ATCC 19111), *Bacillus subtilis* (ATCC 6633) and *Clavibacter michiganensis* (plant tissue isolate), and four Gram-negative strains, *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922), *Pseudomonas syringae* (CFBP 2473) and *Xanthomonas arboricola* (plant tissue isolate). The bacterial strains were cultured in MHB and MHA (Mueller–Hinton broth and agar, HiMedia, Mumbai, India), except for *L. monocytogenes* that was cultured in BHI broth (Brain–Heart Infusion, Biomedics, Madrid, Spain). Incubation lasted 24 h at a temperature of 37 °C, except for *P. syringae*, *X. arboricola* and *C. michiganensis* that were grown at 30 °C. Bacterial suspensions were adjusted to McFarland standard turbidity (0.5) (BioMérieux, Marcy-l'Étoile, France), which corresponds to 10^{7}–10^{8} CFU mL^{-1}.

Preparation of the methanol extract

For chemical analysis, dried and ground plant material (5 g) was extracted in 50 mL of methanol (MeOH). The extraction took place in the dark for 24 h. Extraction in the first and last hour of the scheduled time was performed in an ultrasonic bath. After filtration and washing with MeOH, the extracts were evaporated using a rotary vacuum evaporator (Laborota 4001, Heidolph) at 40 °C. The yields of the obtained extracts were: *M. polymorpha* – 0.080 g (8.0 %), *C. conicum* – 0.066 g (6.6 %) and *P. endiviifolia* – 0.036 g (3.6 %). The extracts were packed in vials and stored at 4 °C until use.

Chemical analysis

Chemical analysis of MeOH extract was performed using nuclear magnetic resonance at the Faculty of Chemistry, University of Belgrade. The ^{1}H-NMR spectra of the MeOH extracts were recorded on a Bruker Avance III 500 spectrometer at 500.26 MHz in CD_3OD as the solvent, and TMS (tetramethylsilane) as the reference compound.

Determination of the antimicrobial activity

Well diffusion method. The well diffusion method was performed according to Dimkic *et al.*,[6] and used for the screening of the antibacterial activity of liverwort extracts. Sterile molds for the wells (5 mm in diameter) were placed with sterile tweezers on the MHA which was used as the solid medium. The MHA/BHI soft agar was melted, cooled to 47 °C, inoculated with 100 μL of bacterial suspension and poured onto MHA plates. After solidification, the well molds were pulled out with sterile tweezers thus creating wells. Extracts of *M. polymorpha*, *C. conicum*, *P. endiviifolia*, and marchantin A were dissolved in DMSO solvent and 10 μL of each solution was added to the wells. The antibiotic streptomycin was used as the positive control. The Petri dishes were incubated for 24 h at 37 °C, except for *P. syringae*, *X. arboricola* and *C. michiganensis* that were incubated at 30 °C. The results were analyzed by measuring the diameter of the bacterial growth inhibition zone (mm).

MIC assay. The minimum inhibitory concentrations (*MIC*) and minimum bactericidal concentrations (*MBC*) of MeOH extracts of *M. polymorpha*, *C. conicum*, *P. endiviifolia*, and marchantin A dissolved in DMSO solvent were tested using the broth microdilution method.[7] Two-fold serial dilutions with MHB medium in 96-well microtiter plates were performed, apart from *L. monocytogenes*, for which BHI medium was used. The final concentrations of all three tested extracts were 5 mg mL^{-1} (range of tested concentrations were 5–0.039 mg mL^{-1}), while for marchantin A, the concentration was 1 mg mL^{-1} (range of tested concentrations were 1–0.008 mg mL^{-1}). The final concentration of DMSO as the solvent was 10 %. The antibiotic streptomycin (Sigma–Aldrich, Carlsbad, CA, USA) was tested as the positive control in a final concentration 0.2 mg mL^{-1}. All dilutions were performed in duplicate. Each well, except for the sterility control, was inoculated with 20 μL of bacterial culture (approx. 10^{8} CFU mL^{-1}), reaching a final volume of 200 μL. Finally, 22 μL of resazurin (0.675 mg mL^{-1}) was added to each well. The plates were incubated for 24 h at 37 °C for all strains except for *P. syringae*, *X. arboricola* and *C. mitchiganensis* that were incubated at 30 °C. The lowest concentration that showed no change in the resazurin color was defined as the *MIC*. The MBC was determined by sub-culturing the test dilutions from each well without color change on agar plates and incubating for 18–24 h, and the lowest concentration that did not show any bacterial growth was defined as the *MBC* value.

RESULTS AND DISCUSSION

Chemical characterization

Based on the ^{1}H-NMR analyses, it was concluded that the MeOH extract of *M. polymorpha* contained terpenes, oils, sugars (free or bound as glycosides), and bis-bibenzyls (marchantin A as one of the most dominant) (Fig. 1) as the main groups of chemical compounds.

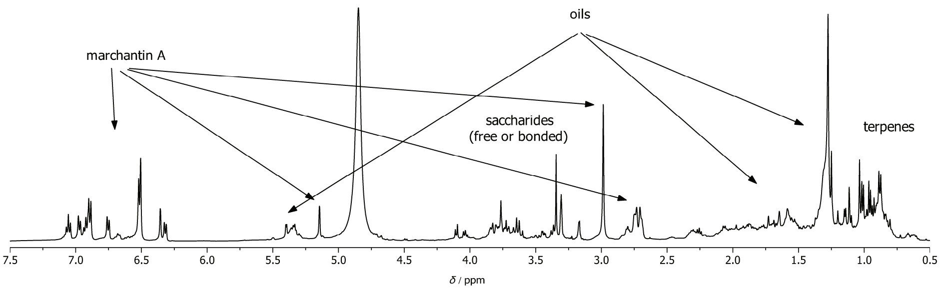

Fig. 1. ^{1}H-NMR spectrum of the *M. polymorpha* MeOH extract.

Marchantin A (Figs. 2 and 3) is a cyclic bis-bibenzyl previously isolated from different *Marchantia* species, *Plagiochasma appendiculatum* and *Wiesnerella denudata.* This is the most common bis-bibenzyl in *M. polymorpha*.[5] The content of marchantin A can be up to 60 g kg^{-1} of plant material.[5] The ^{1}H-NMR spectrum of the present methanol extract of *M. polymorpha* showed almost only marchantin A in the aromatic part, suggesting a high amount of this bibenzyl (Fig. 2).

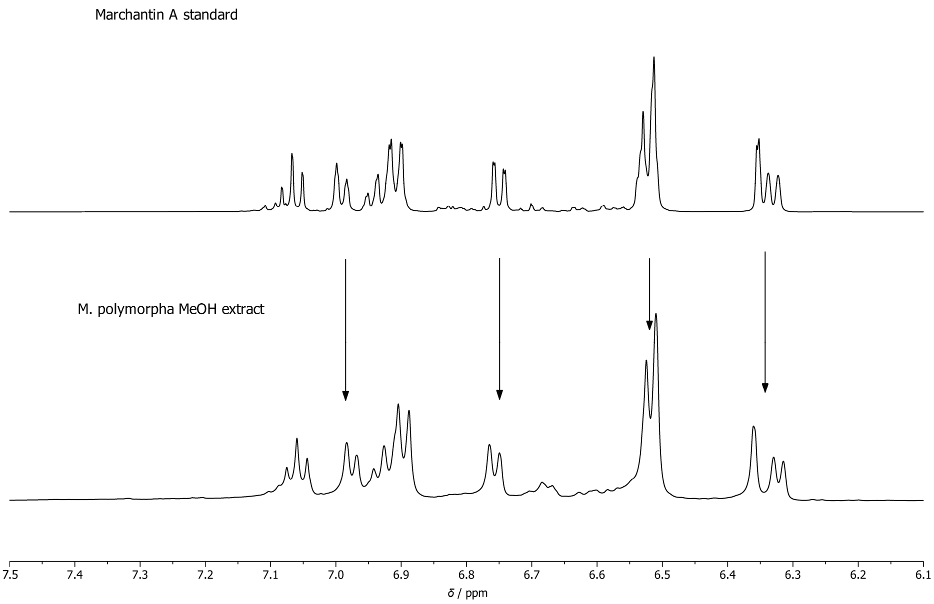

Fig. 2. Matched aromatic parts of the ^{1}H-NMR spectra of MeOH extracts *M. polymorpha* and standard marchantin A.

Based on the ^{1}H-NMR spectrum, it could be concluded that the MeOH extract of *C. conicum* contained terpenes, oils, and sugars (free or bound as glycosides, Fig. 4). According the literature, mainly monoterpenic esters,[8] sesquiterpene lactones[9] and phenethyl glycosides[10] were isolated from this liverwort, but not macrocyclic bis-bibenzyls. On the other hand, species from the same genus, *C. japonicum*, synthesized macrocyclic bis-bibenzyls, perrottetin E, isoriccardin C, marchantin A, marchantin E, marchantin C and isomarchantin C.[11]

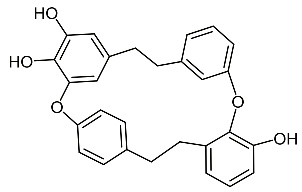

Fig. 3. Chemical structure of marchantin A.

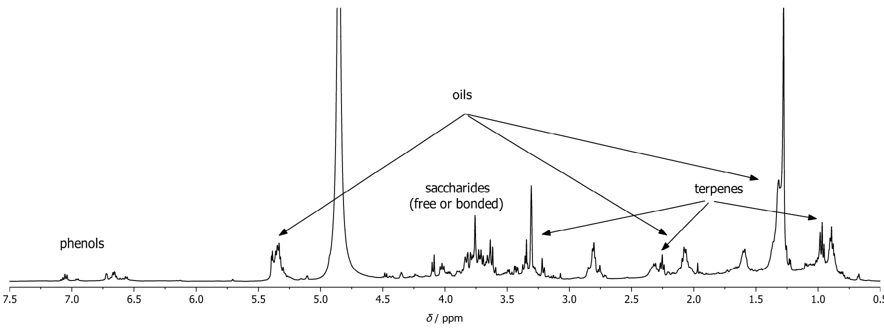

Fig. 4. ^{1}H-NMR spectrum of a MeOH extract of *C. conicum*.

According to the ^{1}H-NMR analyses, it could be proposed that the MeOH extract of *P. endiviifolia* contained terpenes, oils, sugars (free or bound as glycosides), and bis-bibenzyls as the main groups of chemical compounds (Fig. 5). Previously, few macrocyclic bis-bibenzyls, mainly perrotetins, have been isolated from the dichloromethane/methanol extract of *P. endiviifolia.*[12,13]

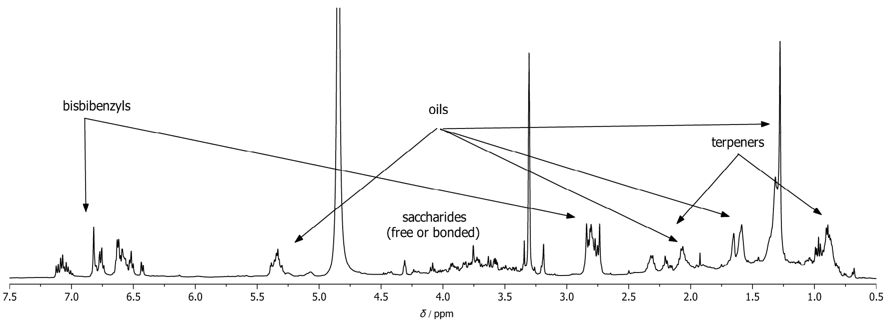

Fig 5. ^{1}H-NMR spectrum of a MeOH extract of *P. endiviifolia*.

Antimicrobial activity of the liverwort extracts

The well diffusion test was used for the initial screening of the antibacterial activity of the liverworts extracts and one active compound marchantin A. Based on the obtained results (Table I), Gram-positive bacteria, except *C. michigenesis*, were sensitive to the tested extracts and marchantin A, while Gram-negative bacteria were resistant to all the tested extracts and the compound. The diameter of the inhibition zone for *B. subtilis*, *S. aureus*, and *L. monocytogenes* ranged from 10–14 mm. The most effective antimicrobial activity was shown by the *M. polymorpha* extract against *B. subtilis* (inhibition zone 14 mm) (Table I and Fig. 6).

TABLE I. The effect of *M. polymorpha*, *C. conicum*, *P. endiviifolia* extracts and marchantin A on the tested bacteria (well diffusion method); NA – no activity

Bacterial culture	Diameter of the inhibition zone, mm
Bacillus subtilis (ATCC 6633)	–
Marchantia polymorpha	14
Conocephalum conicum	NA
Pellia endiviifolia	13
Marchantin A	13
Staphylococus aureus (ATCC 25923)	–
Marchantia polymorpha	11
Conocephalum conicum	NA
Pellia endiviifolia	10
Marchantin A	11
Listeria monocytogenes (ATCC 19111)	–
Marchantia polymorpha	13
Conocephalum conicum	NA
Pellia endiviifolia	12
Marchantin A	12

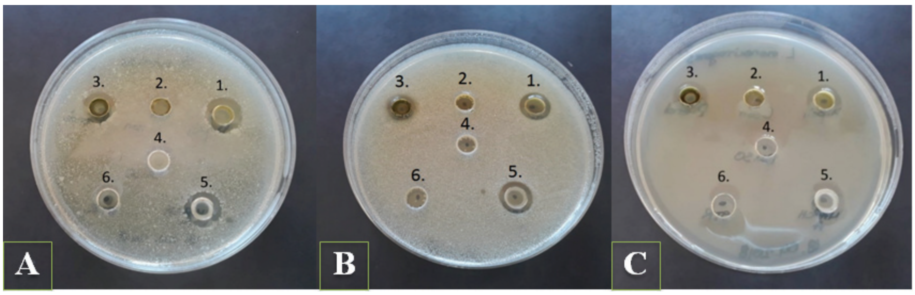

Fig. 6. Inhibition zones: A) *Bacillus subtillis*; B) *Staphylococcus aureus*; C) *Listeria monocytogenes*; 1. *Marchantia polymorpha* MeOH extract; 2. *Conocephalum conicum* MeOH extract; 3. *Pellia endiviifolia* MeOH extract; 4. DMSO; 5. marchantin A; 6. streptomycin.

The MeOH extracts of *M. polymorpha*, *C. conicum*, *P. endiviifolia* and marchantin A used in the *MIC* assay had no antimicrobial effect against Gram-negative bacteria strains. On the other hand, antimicrobial effects were determined against

Gram-positive bacteria (Table II), with the minimum inhibitory concentration (*MIC*) ranging from 0.062 to 5 mg mL^{-1}, and the minimum bactericidal concentration (*MBC*) from 1 to 5 mg mL^{-1}. The most promising antibacterial activity was shown towards *S. aureus* by marchantin A (*MIC* 0.062 mg mL^{-1}). Marchantin A also showed antibacterial effects against *L. monocytogenes* and *B. subtilis*. Both *M. polymorpha* and *P. endiviifolia* extracts showed antibacterial effects against *S. aureus* and *L. monocytogenes*. The antibacterial activity of the methanol extract of *M. polymorpha* cannot be fully ascribed to marchantin A, although it is highly abundant (Fig. 2), since terpenes can contribute to the antibacterial activity.[3] The scientific literature reports various studies in which saccharides have beneficial effects on bacterial control.[14,15] Synergistic effects among the components may also be responsible for the activity.

However, the *C. conicum* extract did not show antibacterial activity against the microorganisms tested. It may be explained by absence of bis-bibenzyls, proved in literature as good antimicrobial agents. Minimum inhibitory concentrations ranging from 0.00625–0.025 mg mL^{-1} and MBC ranging from 0.001562 to 0.025 mg mL^{-1}, proved that tested Gram-positive bacteria were more sensitive to the antibiotic streptomycin than liverwort's extracts and marchantin A (Table II).

TABLE II. Antimicrobial activity of *M. polymorpha, C. conicum, P. endiviifolia* MeOH extracts, marchantin A, and streptomycin on different strains of Gram-positive bacteria

Activity parameter	*S. aureus* (ATCC 25923)	*C. michiganensis* (plant tissue isolate)	*L. monocytogenes* (ATCC 19111)	*B. subtilis* (ATCC 6633)
		Marchantia polymorpha		
MIC / mg mL^{-1}	0.156	–	2.50	–
MBC / mg mL^{-1}	–	–	–	–
Conocephalum conicum				
MIC / mg mL^{-1}	–	–	–	–
MBC / mg mL^{-1}	–	–	–	–
Pellia endiviifolia				
MIC / mg mL^{-1}	0.315	–	5.00	–
MBC / mg mL^{-1}	5.00	–	–	–
		Marchantin A		
MIC / mg mL^{-1}	0.062	–	0.5–1.00[a]	1.00
MBC / mg mL^{-1}	–	–	1.00	–
		Streptomycin		
MIC / mg mL^{-1}	0.025	0.00625	0.0125–0.025[a]	–
MBC / mg mL^{-1}	–	0.025	0.025	0.001562

[a]*MIC* value is between two tested concentrations

In previous investigations bibenzyls from *Radula obconica* showed an antibacterial effect against *B. subtilis* with clear zone, 2.0 cm in disc diffusion assay.[16] Extracts of *Plagiochasma japonica* also show antibacterial activity[17] as well as *Plagiochila stephensoniana.*[18] Bibenzyl lunularin isolated from *Dumortiera hirsuta* inhibits the growth of *P. aeruginosa* (MIC 64 μg mL^{-1}).[19] Antibacterial effect exhibited extracts of *Cylindrocolea recurvifolia* and *Pleurozia subinflata.*[20] Marchantin A isolated from *M. polymorpha*, *M. tosana*, *M. plicata* and *M. chenopoda* displayed antibacterial activity against *B. cereus* (*MIC* 12.5 μg mL^{-1}), *B. subtilis* (25 μg mL^{-1}), *B. megaterium* (25 μg mL^{-1}), *Staphylococcus aureus* (3.13 – 25 μg mL^{-1}), *Enterobacter cloacae*, *Proteus mirabilis*, *E. coli*, *Salmonella typhimurium* (100 μg mL^{-1}), *Alcaligenes faecalis* (100 μg mL^{-1}), *Acinetobacter calcoaceticus* (6.25 μg mL^{-1}), *Cryptococcus neoformans* (12.5 μg mL^{-1}).[21] Methanol extract of *M. polymorpha* was screened against *E. coli*, *Proteus mirabilis* and *S. aureus* and showed the highest activity against *S. aureus*.[22] Extract of *C. conicum* showed activity against *Pseudomonas aeruginosa*,[23] *P. mirabilis* and *Salmonella sp*.[24] Methanol extract of *P. endiviifolia* inhibited the growth of *B. subtilis* (*MIC* 0.01–0.19 mg mL^{-1}),[23] as well as *S. aureus* (*MIC* 1.0 to 1.25 mg mL^{-1}).[26] Nikolajeva *et al.*[27] investigated the aqueous extract of *M. polymorpha* and concluded no influence on the growth of *S. aureus*, although in literature data can be found about the antibacterial influence of this liverwort species on Gram–positive bacteria among others.[25] This is contrary to investigation of Kamory *et al*.[28] where is highlighted effectiveness of marchantin A on Gram–negative strains *Pseudomonas aeruginosa* 170006 (*MIC* = 85.4 nM), and *Pasteurella multocida* 96101 (*MIC* = 4.5 nM). This research also confirms effectiveness of marchantin A on Gram–positive strains (*Streptococcus viridans*, *S. pyogenes*, *S. faecalis* and *S. aureus*),[28] which is in accordance with results obtained in our study. The methanol and flavonoid extracts of *M. polymorpha* showed the highest antimicrobial activity against *S. aureus* (inhibition zones 20.6 and 19.6 mm, *MIC* 0.281 and 0.312 mg mL^{-1}, *MBC* 1.125 and 0.312 mg mL^{-1}, respectively), among three bacterial and four fungal strains tested.[22]

CONCLUSION

^{1}H-NMR analysis indicate the presence of terpenes, oils, sugars, and bis-bibenzyls in the methanol extracts of *M. polymorpha* and *P. endiviifolia* and absence of bis-bibenzyls in *C. conicum* extract. Methanol extracts of *M. polymorpha* and *P. endiviifolia* and marchantin A exhibited antimicrobial activity against Gram-positive bacteria which was confirmed by well diffusion and microdilution methods. The most promising antimicrobial effect was shown by marchantin A against *Staphylococcus aureus.* Methanol extract of *C. conicum* did not show antimicrobial activity against the tested bacterial strains. Marchantin A – the dominant compound in *M. polymorpha*, fulfilled literature data that it possesses significant antibacterial activity. In addition, Gram-positive bacteria showed more sensitivity to the liverwort extracts tested than Gram-negative ones.

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ИЗВОД

АНТИБАКТЕРИЈСКА СВОЈСТВА ТАЛУСНИХ ЈЕТРЕЊАЧА *Marchantia polymorpha* L., *Conocephalum conicum* (L.) DUM. И *Pellia endiviifolia* (DICKS.) DUMORT.

ИВАНА М. ИВКОВИЋ[1], ДАНКА Р. БУКВИЧКИ[1], МИРОСЛАВ М. НОВАКОВИЋ[2], СТЕФАН Г. ИВАНОВИЋ[2], ОЉА Ј. СТАНОЈЕВИЋ[1], ИВАН С. НИКОЛИЋ[1] и МИЛАН М. ВЕЉИЋ[1]

[1]*Универзитет у Београду, Биолошки факултет, Институт за ботанику и Ботаничка башта „Јевремовац", Таковска 43, 11000 Београд и* [2]*Универзитет у Београду – Институт за хемију, технологију и металургију, Центар за хемију, Његошева 12, 11000 Београд*

У овом раду испитиван је хемијски састав и антибактеријска активност метанолних екстраката три јетрењаче, *Marchantia polymorpha*, *Conocephalum conicum* и *Pellia endive-ifolia* и бис-бибензила маршанцина А, доминантне компоненте у метанолном екстракту *M. polymorpha*. ^{1}H-NMR спектроскопија је показала присуство терпена, уља, шећера и бис-бибензила у екстрактима *M. polymorpha* и *P. endiviifolia*, док екстракт *C. conicum* не садржи специфична макроциклична једињења – бис-бибензиле. Антимикробни потенцијал је тестиран на осам бактеријских сојева. Антимикробни ефекат маршанцина А уочен је на све грам позитивне сојеве, док је ефекат изостао код грам негативних сојева у обе тестиране методе – дифузионе методе у бунарима и микродилуционе методе у хранљивом бујону.

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REFERENCES

1. R. M. Schuster, *The Hepaticae and Anthocerotae of North America*, Vol. I, Columbia University Press, New York, NY, 1966 (ISBN: 9780231028141)
2. X. He, Y. Sun, R. L. Zhu, *Crit. Rev. Plant Sci.* **32** (2013) 293 (https://doi.org/10.1080/07352689.2013.765765)
3. Y. Asakawa, A. Ludwiczuk, F. Nagashima, *Phytochemistry* **91** (2013) 52 (https://doi.org/10.1016/j.phytochem.2012.04.012)
4. A. Upadhyay, I. Upadhyaya, A. Kollanoor-Johny, K. Venkitanarayanan, *Biomed Res. Int.* **2014** (2014) 1 (https://doi.org/10.1155/2014/761741)
5. Y. Asakawa, M. Toyota, M. Tori, T. Hashimoto, *J. Spectrosc*. **14** (2000) 149 (https://doi.org/10.1155/2000/570265)
6. I. Dimkić, P. Ristivojević, T. Janakiev, T. Berić, J. Trifković, D. Milojković-Opsenica, S. Stanković, *Ind. Crop. Prod.* **94** (2016) 856 (https://doi.org/10.1016/j.indcrop.2016.09.065)
7. A. Klančnik, S. Piskernik, B. Jeršek, S. Smole Možina, *J. Microbiol. Methods* **81** (2010) 121 (https://doi.org/10.1016/j.mimet.2010.02.004)
8. M. Toyota, *Yakugaku Zasshi* **120** (2000) 1359 (https://doi.org/10.1248/yakushi1947.120.12_1359)
9. Y. Asakawa, T. Takemoto, *Phytochemistry* **18** (1979) 285 (https://doi.org/10.1016/0031-9422(79)80072-2)
10. M. Toyota, T. Saito, Y. Asakawa, *Phytochemistry* **43** (1996) 1087 (https://doi.org/10.1016/S0031-9422(96)00504-3)

11. N. Liu, D. X. Guo, Y. Y. Wang, L. N. Wang, M. Ji, H. X. Lou, *Nat. Prod. Commun*. **6** (2011) 49 (https://doi.org/10.1177%2F1934578X1100600112)
12. T. Hashimoto, H. Suzuki, M. Tori, Y. Asakawa, *Phytochemistry* **30** (1991) 1523 (https://doi.org/10.1016/0031-9422(91)84201-3)
13. I. Ivković, M. Novaković, M. Veljić, M. Mojsin, M. Stevanović, P. D. Marin, D. Bukvički, *Plants* **10** (2021) 1063 (https://doi.org/10.3390/plants10061063)
14. L. Mizzi, D. Maniscalco, S. Gaspari, C. Chatzitzika, R. Gatt, V. P. Valdramidis, *Lett. Appl. Microbiol*. **71** (2020) 251 (https://doi.org/10.1111/lam.13306)
15. J. Chifre, G. Scarmato, L. Herszage, *Lancet* **8271** (1982) 560 (https://doi.org/10.1016/s0140-6736(82)92065-7)
16. K. D. Millar, B. J. Crandal-Stotler, J. F. S. Ferreira, K. V. Wood, *Cryptog. Bryol*. **28** (2007) 197
17. E. H. Lahlou, T. Hashimoto, Y. Asakawa, *J. Hattori Bot. Lab*. **88** (2000) 271 (https://doi.org/10.18968/jhbl.88.0_271)
18. S. D. Lorimer, N. B. Perry, R. S. Tangney, *J. Nat. Prod*. **56** (1993) 1444 (https://doi.org/10.1021/np50099a002)
19. Z. Q. Lu, P. H. Fan, M. Ji, H. X. Lou, *J. Asian Nat. Prod. Res*. **8** (2006) 187 (https://doi.org/10.1080/1028602042000325537)
20. D. Wang, R.-L. Zhu, L. Qu, *Cryptog. Bryol*. **27** (2006) 343
21. Y. Asakawa, in *Phytochemicals in Human Health Protection, Nutrition, and Plant Defense*, J. Romeo, Ed., Kluwer Academic/Plenum Publishers, New York, NY, 1999, p. 319 (https://doi.org/10.1007/978-1-4615-4689-4_12)
22. N. Mewari, P. Kumar, *Pharm. Biol*. **46** (2008) 819 (https://doi.org/10.1080/13880200802315725)
23. M. Singh, S. Singh, V. Nath, V. Sahu, A. K. S. Rawat, *Pharm. Biol*. **49** (2011) 526 (https://doi.org/10.3109/13880209.2010.523007)
24. R. Castaldo-Cobianchi, S. Giordano, A. Basile, U. Violante, *G. Bot. Ital*. **122** (1988) 303 (https://doi.org/10.1080/11263508809429412)
25. M. Vujicic, I. Dimkic, A. Sabovljević, S. Stankovic, M. Sabovljević, *Acta Biol. Planta Agrien*. **5** (2017) 63 (https://doi.org/10.21406/abpa.2017.5.1.63)
26. A. Dey, S. Mukherjee, A. De, *J. Herbs Spices Med. Plants* **21** (2015) 102 (https://doi.org/10.1080/10496475.2014.918915)
27. V. Nikolajeva, L. Liepina, Z. Petrina, G. Krumina, M. Grube, I. Muiznieks, *Adv. Microbiol*. **2** (2012) 345 (https://doi.org/10.4236/aim.2012.23042)
28. E. Kamory, G. M. Keseru, B. Papp, *Planta Med*. **61** (1995) 387 (https://doi.org/10.1055/s-2006-958116).