applied sciences

MDPI

Editorial

Advances in Natural Antimicrobial Compounds: Discovery, Synthesis, Characterization, and Application

Ramona Iseppi * and Carla Sabia

Department of Life Sciences, University of Modena and Reggio Emilia, Via G. Campi 287, 41125 Modena, Italy; carla.sabia@unimore.it

* Correspondence: ramona.iseppi@unimore.it; Tel.: +39-059-205-5469

1. Introduction

Antimicrobial resistance is increasingly recognized as a major threat to the prevention and treatment of a growing number of infections. Therefore, there is an urgent need to promote the discovery and development of new therapeutic antibacterial agents to combat the ongoing antibiotic resistance crisis [1,2]. In parallel, significant progress has been achieved in the synthesis and structural optimization of natural antimicrobial compounds, enabling the development of derivatives with improved efficacy, enhanced stability, and reduced toxicity. Modern analytical techniques, including mass spectrometry (MS), nuclear magnetic resonance (NMR), and next-generation sequencing (NGS), have greatly advanced the characterization of these bioactive molecules and their mechanisms of action [3–5]. Natural antimicrobials have demonstrated activity not only against planktonic microorganisms but also against biofilms and virulence-associated pathways, offering promising alternatives to conventional antibiotics [6]. Furthermore, the application of natural antimicrobial compounds extends beyond clinical medicine to food preservation, agriculture, environmental protection, and the One Health framework, highlighting their potential contribution to sustainable strategies for controlling microbial contamination and infectious diseases [7–10]. Advances in the discovery, synthesis, characterization, and application of natural antimicrobial compounds are expected to play a crucial role in addressing the growing threat of antimicrobial resistance and fostering the development of innovative therapeutic solutions.

2. An Overview of Published Articles

This Special Issue brings together original research articles and reviews that highlight recent advances in the identification, characterization, and application of natural antimicrobial agents. A comprehensive review examined the potential of essential oils as natural antibiofilm agents to combat biofilm-associated infections, a major challenge in the era of antimicrobial resistance. The ability of essential oils and their bioactive constituents to alter microbial membranes, interfere with quorum sensing, and inhibit biofilm formation in a wide range of bacterial pathogens was highlighted. Particular attention was given to their synergistic interactions with conventional antibiotics, which can improve therapeutic efficacy while reducing antibiotic use. Overall, the review emphasized the potential of essential oils as complementary strategies for the prevention and control of biofilm-mediated infections, while also highlighting the need for further research to support their safe and effective clinical application (contribution 1).

Regarding essential oils, Hristova et al. evaluated the antifungal activity of *Origanum heracleoticum* L. essential oil against clinical *Candida* isolates, including fluconazole-resistant

Received: 15 June 2026
Accepted: 23 June 2026
Published: 26 June 2026

strains. The essential oil showed significant antifungal activity against all isolates tested and was shown to influence fungal membrane integrity and virulence-related traits, such as germination and filamentation. These results highlight the potential of *O. heracleoticum* L. essential oil as a promising natural source of antifungal agents for the management of drug-resistant *Candida* infections, warranting further investigation of its clinical applicability (contribution 2).

Another contribution evaluated the antibacterial activity of carvacrol against multidrug-resistant Gram-negative clinical isolates recovered from chronic wound infections, including carbapenemase-producing strains. Carvacrol treatment increased the production of reactive oxygen species (ROS), suggesting that oxidative stress may contribute to its antimicrobial activity (contribution 3). ROS were also implicated in the antibacterial activity observed against *Staphylococcus aureus* and *Escherichia coli* when grapevine leaf extracts are subjected to photodynamic (PDT) and sonodynamic (SDT) treatments. Among the identified bioactive constituents, quercetin 3′-O-glucuronide and pheophorbide a were indicated as potentially playing a key role in the observed effects. The results highlight the potential of combining plant-derived extracts with PDT and SDT technologies as innovative and sustainable approaches for microbial control in food, environmental, and healthcare applications (contribution 4).

Continuing the exploration of plant-derived antimicrobials, a study evaluated the antibacterial potential of extracts and epifriedelanol isolated from *Synadenium glaucescens* against *S. aureus*. In addition to confirming the antimicrobial activity of these plant-derived compounds, the study identified bacterial fitness genes associated with natural resistance, highlighting the role of gene *hemB* in modulating bacterial susceptibility. These findings further support the potential of medicinal plants as sources of novel antimicrobial agents, while also providing new insights into bacterial responses to natural products (contribution 5).

An additional application of essential oils is their incorporation into food-packaging materials to extend product shelf life. Jankowski et al. evaluated the antimicrobial and antiviral activity of tea tree oil (TTO)-based coatings applied to polypropylene films before and after Q-SUN accelerated aging. The coatings showed antibacterial effects against several pathogens and strong antiviral activity against bacteriophage Φ6, maintaining their efficacy even after the aging treatment. These results support the potential of essential oil-based active packaging materials to improve microbiological safety in food and environmental applications (contribution 6).

In the context of sustainable bioeconomy approaches, a study examined the use of agro-industrial residues as substrates for the cultivation of *Epicoccum nigrum*. Various lignocellulosic by-products successfully supported fungal growth and the production of bioactive extracts exhibiting both enzymatic (α-amylase and cellulase) and antifungal activities. The extracts demonstrated inhibitory effects against several phytopathogenic fungi, highlighting the potential of *E. nigrum* as a source of biologically active compounds. These findings emphasize the feasibility of converting agricultural waste into value-added products, supporting circular economy strategies and the development of sustainable biotechnological and agricultural applications (contribution 7).

Finally, a comprehensive review examined the potential of natural antimicrobial compounds in companion animal medicine as alternative or complementary tools to address antimicrobial resistance within the One Health framework. The authors discussed a wide range of bioactive agents, including antimicrobial peptides, phytochemicals, enzymatic proteins, probiotics, prebiotics, and nutraceuticals, highlighting their mechanisms of action, therapeutic applications, and current limitations. The review emphasized the growing relevance of natural compounds in reducing antibiotic use in dogs and cats, while underscoring

the need for further clinical validation, safety assessments, and standardized formulations to support their broader implementation in veterinary practice (contribution 8).

3. Conclusions

The contributions collected in this Special Issue demonstrate the growing importance of natural antimicrobial compounds as valuable resources for combating antimicrobial resistance and improving microbial control in clinical, veterinary, agricultural, environmental, and food-related settings. Collectively, these studies highlight the diversity of natural bioactive molecules, their mechanisms of action, and their wide range of applications. The findings presented herein further support the development of innovative, sustainable, and effective antimicrobial strategies based on natural products and encourage future interdisciplinary research in this rapidly evolving field.

Author Contributions: R.I.: writing—original draft preparation; C.S.: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Acknowledgments: Thanks to all the contributing authors for their interest and support, and peer reviewers for their essential contributions to the Special Issue "Advances in Natural Antimicrobial Compounds: Discovery, Synthesis, Characterization, and Application".

Conflicts of Interest: The authors declare no conflicts of interest.

List of Contributions

1. Nurzyńska-Wierdak, R. Antibiofilm Potential of Natural Essential Oils. *Appl. Sci*. 2025, *15*, 5847. https://doi.org/10.3390/app15115847.
2. Hristova, Y.; Iliev, I.; Hristamyan, M.; Gocheva, M.; Ilieva, L.; Gochev, V. Antimycotic Activity of Essential Oil of *Origanum heracleoticum* L. from Bulgaria Against Clinical Isolates of *Candida* spp. *Appl. Sci.* **2025**, *15*, 11672. https://doi.org/10.3390/app152111672.
3. Pruss, A.; Lichota, A.; Masiuk, H.; Kwiatkowski, P.; Słaba, M.; Sienkiewicz, M.; Dołęgowska, B. Evaluation of the Effects of Carvacrol on Gram-Negative Bacilli Isolated from Wound Infections. *Appl. Sci.* **2025**, *15*, 11309. https://doi.org/10.3390/app152111309.
4. Ale, T.H.; Hovor, I.; Atrash, M.; Semenova, O.; Zemliana, N.; Kogan, N.M.; Nisnevitch, M.; Nakonechny, F. Photodynamic and Sonodynamic Antibacterial Activity of Grape Leaf Extracts. *Appl. Sci.* **2025**, *15*, 10738. https://doi.org/10.3390/app151910738.
5. Msengwa, Z.; Bojer, M.S.; Rwegoshora, F.; Mwesongo, J.; Mafuru, M.; Mabiki, F.P.; Mwang'onde, B.J.; Mtambo, M.M.; Kusiluka, L.J.; Christensen, H.; et al. Mutation Rates and Fitness Genes in *Staphylococcus aureus* Treated with the Medicinal Plant *Synadenium glaucescens*. *Appl. Sci.* **2025**, *15*, 8753. https://doi.org/10.3390/app15158753.
6. Jankowski, W.; Mizielińska, D.; Mizielińska, M. Influence of Q-SUN Irradiation on Antimicrobial and Antiviral Activity of Tea Tree Oil-Based Coatings on Polypropylene Films. *Appl. Sci.* **2025**, *15*, 10017. https://doi.org/10.3390/app151810017.
7. Ganeva, Z.; Goranov, B.; Brazkova, M.; Blazheva, D.; Baldzhieva, R.; Stefanova, P.; Slavov, A.; Denkova-Kostova, R.; Bozhkov, S.; Angelova, G. Agro-Industrial Residues as Cost-Effective and Sustainable Substrates for the Cultivation of *Epicoccum nigrum*, with Insights into Growth Kinetic Characteristics and Biological Activities. *Appl. Sci.* **2025**, *15*, 10571. https://doi.org/10.3390/app151910571.
8. Vercelli, C.; Amadori, M.; Gambino, G.; Danieli, D.; Crimi, S.; Re, G. Natural Antimicrobial Compounds in Veterinary Medicine: Focus on Companion Animals. *Appl. Sci.* **2025**, *15*, 12388. https://doi.org/10.3390/app152312388.

References

1. Medema, M.H.; van Wezel, G.P. New Solutions for Antibiotic Discovery: Prioritizing Microbial Biosynthetic Space Using Ecology and Machine Learning. *PLoS Biol.* **2025**, *23*, e3003058. [CrossRef] [PubMed]
2. Stan, D.; Enciu, A.M.; Mateescu, A.L.; Ion, A.C.; Brezeanu, A.C.; Stan, D.; Tanase, C. Natural Compounds With Antimicrobial and Antiviral Effect and Nanocarriers Used for Their Transportation. *Front. Pharmacol.* **2021**, *12*, 723233. [CrossRef] [PubMed]
3. Cieśla, Ł.; Moaddel, R. Comparison of Analytical Techniques for the Identification of Bio-active Compounds From Natural Products. *Nat. Prod. Rep.* **2016**, *33*, 1131–1145. [CrossRef] [PubMed]
4. Gaudêncio, S.P.; Bayram, E.; Lukić Bilela, L.; Cueto, M.; Díaz-Marrero, A.R.; Haznedaroglu, B.Z.; Jimenez, C.; Mandalakis, M.; Pereira, F.; Reyes, F.; et al. Advanced Methods for Natural Products Discovery: Bioactivity Screening, Dereplication, Metabolomics Pro-filing, Genomic Sequencing, Databases and Informatic Tools, and Structure Elucidation. *Mar. Drugs* **2023**, *21*, 308. [CrossRef] [PubMed]
5. Pereira, R.; Anjos, I.; Reis, J.; Dias, C.; Leitão, J. Next-Generation Sequencing (NGS) Identified Species-Specific SSR and SNP Markers, Allow the Unequivocal Identification of Strawberry Tree (*Arbutus unedo* L.) Germplasm Accessions and Contribute to Assess Their Genetic Relationships. *Plants* **2023**, *12*, 1517. [CrossRef] [PubMed]
6. Yuan, Y.; Sun, J.; Raka, R.N.; Liu, Z.; Zhang, Z.; Xiao, J.; Wu, H. Multitarget Inhibitory Effects of Lemongrass Essential Oil on *Porphyromonas gingivalis*: Synergistic Regulation Of Heme Utilization, Biofilm Formation, and The Metabolic Pathway of Ferroptosis. *BMC Complement. Med. Ther.* **2025**, *25*, 449. [CrossRef] [PubMed]
7. Anand, K.; Suprativ, D.; Sadaqat, A.; Swapnil, G.J.; Ahmad, R.; Syed, M.E.R.; Ramachandran, C.; Deog-Hwan, O.; Shucheng, L.; Shuai, W. Mechanisms, Applications and Challenges of Natural Antimicrobials in Food System. *Food Biosci.* **2025**, *74*, 107864. [CrossRef]
8. Alzain, M.; Daghistani, H.; Shamrani, T.; Almoghrabi, Y.; Daghistani, Y.; Alharbi, O.S.; Sait, A.M.; Mufrrih, M.; Alhazmi, W.; Alqarni, M.A.; et al. Antimicrobial Peptides: Mechanisms, Applications, and Therapeutic Potential. *Infect. Drug Resist.* **2025**, *18*, 4385–4426. [CrossRef] [PubMed]
9. Bucataru, C.; Ciobanasu, C. Antimicrobial Peptides: Opportunities and Challenges in Overcoming Resistance. *Microbiol. Res.* **2024**, *286*, 127822. [CrossRef] [PubMed]
10. Robles Ramirez, O.; Osuna, G.; Plisson, F.; Barrientos-Salcedo, C. Antimicrobial Peptides in Livestock: A Review with a One Health Approach. *Front. Cell. Infect. Microbiol.* **2024**, *14*, 1339285. [CrossRef] [PubMed]