

## COMMENTARY

**Commentary on “Antimicrobial Capacity of Plant Polyphenols against Gram-positive Bacteria: A Comprehensive Review” authored by Enrique Barraón-Catalán, Institute of Molecular and Cell Biology (IBMC), Miguel Hernandez University (UMH), Avda. Universidad s/n, Elche 03202. Spain**Wolf-Rainer Abraham<sup>1</sup><sup>1</sup>*Helmholtz Center for Infection Research, Chemical Microbiology, Inhoffenstrasse 7, 38124 Braunschweig, Germany*

We are facing the emergence and extensive spread of antimicrobial resistance of many pathogens against commercial antibiotics [1]. In addition to this, most microorganisms protect themselves by forming biofilms where cells are glued together by a highly structured, self-produced matrix consisting of a complex mixture of polysaccharides, proteins, lipids and DNA [2]. In biofilms cells are not only well protected but they also produce a number of pathogenicity factors and become much more resistant against antibiotics [3] or the immune system of the host. Hence, pathogens organized in biofilms are very difficult to eradicate [4, 5].

Because i) the resistances against many antibiotics are increasing, ii) less and less new antibiotics are brought into the market, and iii) antibiotics are not effective against biofilm forming pathogens alternatives are urgently needed to control bacterial infections [6, 7]. Especially Gram-positive bacteria with their multiresistances are a challenge in the clinics. One strategy of searching for novel drugs is to look for solutions developed by other organisms. As all multicellular organisms are challenged by pathogenic microorganisms forming biofilms on their body they developed a multitude of compounds for their control [8]. For example, several medicinal plants from Cameroon displayed broad bacteriostatic activities [9], a sponge colonizing *Penicillium* sp. forms the chlorinated polyketide, *Hypoxylon fragiformis* produces sclerin acting against *Staphylococcus aureus* biofilm formation [10] or carolactone from the myxobacterium *Sorangium cellulosum* damages *Streptococcus mutans* biofilms [11], only to mention a few compounds.

That plants are a source for antimicrobials is known for centuries [12], therefore, Álvarez-Martínez and co-workers reviewed the activity of polyphenols from plants against Gram-positive bacteria [13]. This is a really challenging task because a huge chemical diversity of polyphenolic natural products from plants is known and many of these compounds have multiple targets in the cells acting as antioxidants, anticancer drugs, antivirals, etc. besides being antimicrobials. On top of this several antimicrobial natural products have been reported to have several targets in the cells reducing the risk that pathogens develop resistance [14]. The authors were aware of these problems and tackled them by a consequent organization of their review. They limited their review to Gram-positive bacteria but included both planktonic and sessile cells. With this, their scope was much broader than a similar but shorter review only on the antibiofilm activity of polyphenols [15]. The authors nicely compiled various reports on the antibacterial activities of a number of polyphenols. Unfortunately, the current research focus seems to be on *Staphylococcus aureus* and its various multiresistant strains, e. g. MRCA. This is also mirrored in the review but the authors tried to broaden the spectrum of antimicrobial activities against Gram-positive bacteria wherever it was possible. They also dealt very well with the “grey zone” of reports were ill characterized mixtures of polyphenols have been tested against Gram-positive bacteria. As from the broad diversity of chemical structures can be expected polyphenols from plants have several modes of action. Most screenings for antibiofilm compounds focus on the communication of the bacterial cells to form a biofilm, the quorum sensing

cascade. This, however, misses all the other targets which control biofilm formation and dispersion [16]. The authors were aware of this bias and, where available, they compiled the different mechanisms offering insights into the many ways for the control of Gram-positive bacteria. Such an overview over the mechanisms is very valuable, on the one hand for the set-up of sophisticated screening assays but also on the other hand to broaden the antimicrobial spectrum of bioactive natural compounds.

In my opinion the complex biofilm communities of the oral cavity is a hot topic but not much has been said on dental biofilms where Gram-positive bacteria have a leading role [17]. Not all members of these communities, however, are pathogenic. Some of them may even have a protective role for the teeth. The aim is therefore to control these biofilms and to suppress its pathogenic members. For the control a number of polyphenols have been applied either as pure compounds or as plant extracts [18]. The field of dental biofilms is a nice example where functional food [19], traditional medicine [20, 21] and modern health care [22] meet.

I would like to emphasize another aspect in the search for the optimal antimicrobial polyphenol which was also not much discussed due to space limitation. This is the analyses of the antimicrobial activities of a series of compounds and their connection with the substitution pattern and physical characteristics [23, 24]. These structure activity relationships can lead to improved drugs for the control of pathogens or biofilm infections [25]. Here natural products chemistry meets combinatorial chemistry for the development of natural products for clinical applications [26, 27]. Finally, one should be aware that most of these polyphenols from plants possess only weak to moderate antimicrobial activities. Combining them with commercial antibiotics may boost their activity and may even be effective in biofilm infections [28]. Using combination of different polyphenols, however, requires tight control of their ratios for optimal biological activities as has been mirrored by the variability of results from studies using crude extracts [29]. This faces the problem of standardization of plant extracts both in storage and processing [30, 31].

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