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In Vitro Antimicrobial Activity of Natural Products Using Minimum Inhibitory Concentrations: Looking for New Chemical Entities or Predicting Clinical Response

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Abstract

In previous comments, the difficulties and technical problems of selectivity criteria was exposed related to the antimicrobial activity of extracts plants and pure compounds based in MICs, opening an interesting discussion about this topic. In this way, this commentary seeks to give more elements that feed the proposed debate.

Keywords: Antimicrobial drug discovery; MIC; Selectivity criteria

World Health Organization has determined antimicrobial resistance as public health problem around the world causing increase of morbidity and mortality. Few new antimicrobial drugs have been developed in recent years, for that reason Infectious Society Disease of America (IDSA) launched 10x20 initiative as collaborative effort for obtaining ten new anti-infective drugs for 2020 year [1]. Historically, natural products has been an important source of new chemical scaffolds for drug development, bioprospecting programs looking for agents against multidrug resistant microorganisms is a commitment of the countries with high biodiversity in collaboration with pharmaceutical industry under Nagoya Protocol [2]. In this search, *in vitro* antimicrobial screening of extracts from medicinal plants and microorganisms as well as fractions and pure compounds is fundamental in the development of a drug useful in clinical practice [3].

In vitro antimicrobial screening has two important decisions to make when performing studies on the activity of biodiversity. First, the bioassay selection and second, the selectivity criteria for selection of the promising material for future research. In the bioassay selection, the definitive solution is to select microorganisms that are of public health concern (e.g., Malaria, HIV, Tuberculosis, and MRSA) and use screening platforms reproducible, robust and automatable as far as possible [4], remembering that reproducibility is the only feature that should be preserved, in natural products the methods that use dilution broth techniques are preferred because they have minor problems in diffusion and evaporation [5]. At this point in the experimental design, where they play an important role, the protocols are developed by Clinical and Laboratory Standard Institute (CLSI), but is important take in consideration that these methods were designed for to have information about breakpoints, that by classifying the resistant and susceptible microorganisms, are a guide for the clinical physician in the selection of adequate treatment, these breakpoints are result in the correlation between Minimum Inhibitory Concentration (MIC) and clinical outcome [6].

Use MICs as selectivity criteria of new antimicrobials is a common practice with determined values for drug development. To be considered a promising activity, a crude extract must demonstrate a MIC under 100 µg/m land a pure compound of 4 to 16 µg/ml with optimal value of ≤1 µg/ml [7-9]. But is necessary to include secondary assays for promoting the activity, as susceptibility of resistant clinicalisolates and determination of minimum microbicidal concentrations in time kill curves using concentrations corresponding to 2-4 MICs values, considering a decreasing of 3 $\log_{10}$ colonies forming units (CFU)/ milliliter in comparison with the starting inoculumnear to the original MIC as the optimal value[10,9]. Introducing secondary assays have several advantages as quality control of bioassays, because extracts and compounds can alter the MIC endpoint lecture in liquid culture, equally quality control strains are more susceptible to be inhibited that resistant clinical isolates, due to these microorganisms present adaptive changes to anti-infective agents as cell wall thickening[11,12].

In antimicrobial drug discovery from natural products sources, MICs must not be analysed as isolated data should be used for initial screening as well as for the selection of the material that continue in the secondary assays and target identification research. MICs is the starting point in a bioprospecting program, for that reason their protocols to obtain must be implemented using international standards, because it takes into account the intrinsic target activity and the ability of the extract, fraction or compound to penetrate into the microorganism, important information in the searching of new drugs from biodiversity [9]. The next step is to achieve methods that permit to evaluate MIC in live infection model that can offer an increased capacity of selection, an important advance in this way is the use of *Caenorhabditiselegans* nematode, but it should perform a correlation between the selection index and *in vivo* antimicrobial activity to validate widely [13,14].

This letter seeks to open a discussion to develop solid parameters for screening of obtaining new antimicrobial drugs from biodiversity.

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