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Mechanistic Studies of Cytotoxicity Induced by a Portuguese Propolis Extract, Using Saccharomyces cerevisiae as Eukaryotic Cell Model

Hugo ALVES[1], Catarina PASSÃO[1*], Maria João SOUSA[1,4], Cristina Almeida AGUIAR[1,2,3,4], Ana CUNHA[1,2,3,4] Rui Pedro OLIVEIRA[1,2,3,4]

[1] Biology Department, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal
[2] Centre for the Research and Technology of Agro-Environmental and Biological Sciences (CITAB), Biology Department, Minho University, 4710-057 Braga, Portugal
[3] CEB - Centre of Biological Engineering, University of Minho, 4710-057 Braga, Portugal.
[4] CBMA - Centre of Molecular and Environmental Biology, University of Minho, 4710-057 Braga, Portugal.

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***Corresponding author** /Yazışılan yazar

Abstract

Propolis is a natural complex mixture produced by honey bees (particularly *Apis mellifera* L.) by collecting exudates from various plant sources. Characterized by a plethora of chemicals, propolis is generally rich in flavonoids, phenolic acids and terpene derivatives, bioactive compounds associated to it's antimicrobial, anti-inflammatory, antimutagenic and antioxidant activities[1]. Previous work had shown that the ethanol extract of a sample from the Portuguese region of Beira Alta exhibited unique dual genotoxic and antigenotoxic effects using the yeast *S. cerevisiae* eukaryotic model[2]. In this work we prepared two ethanol extracts (EE) of propolis samples from Pereiro (P) - Beira Alta - collected in 2010 (P10.EE) and 2017 (P17.EE) to investigate the mechanisms of cytotoxicity and genotoxicity using specific *S. cerevisiae* mutants. While P17.EE didn't show any toxic effect, yeast cells exposed to P10.EE showed a considerable decreased viability along time, assessed by colony-forming units. Interestingly, the oxidative stress response-defective mutant *yap*1 was more resistant than the wild type, suggesting that this cytotoxic effect was not mediated by oxidative stress. P.EE's genotoxicity was also analysed by the nucleus-cytosolic translocation of NHP6A protein, considered a marker of necrosis. P10.EE induced NHP6A protein translocation to the cytoplasm, observed by fluorescence microscopy, suggesting that cytotoxicity of this extract was indeed mediated by necrosis. Although P17.EE didn't seem to induce necrotic cell death, both extracts induced plasma membrane integrity loss, assessed by flow cytometry, using propidium iodide as marker. As recently observed for erythroleukemic cells with Brazilian propolis[3], here we present the first evidence that also Portuguese propolis have necrotic-mediated cytotoxicity in yeast cells.

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