Combination of different types of propolis immunomodulates neutrophil response and has antimicrobial effects on *Paracoccidioides brasiliensis*

Lauana Aparecida Santos[1]; Julia Castro Dutra[1]; Thayana Dutra de Andrade[1]; Enrico Picoli Marinho[1]; Masaharu Ikegaki[1]; Rinaldo Poncio Mendes[2]; Eva Burger[1*].

[1]Federal University of Alfenas (UNIFAL-MG), Alfenas, MG, Brazil
[2] Paulista State University, Botucatu (UNESP), SP, Brazil.
[*] Presenting Author. Email: eva.burger@unifal-mg.edu.br

Introduction: Paracoccidioidomycosis (PCM) is severe mycosis caused by fungi of the *Paracoccidioides brasiliensis (P. brasiliensis)* complex. The treatment of PCM is long and complicated. Research for new drugs is limited, so complementary therapies are extremely important.
Different types of propolis-(PBGR) have great economic and medicinal importance. Propolis is identified according to its color, green, brown or red.

Objectives: To evaluate whether PBGR improves neutrophils (PMNs) activation state and antifungal activity against the virulent Pb18 *P. brasiliensis* isolate.

Methods: Antifungal activity of PBGR at a concentration of 500mg/mL was tested using the macrodilution technique. For PMN activation state evaluation, mice (Animal Ethics Committee Protocol 25/2018) were inoculated subcutaneously (sc) in the air-pouch with Pb18. On the 5th day of infection, treatment with 500mg/mL PBGR by the same route was initiated and maintained for 3 days until collection of the PMNs at 8 days of infection and treatment.
The following parameters were analyzed: absolute number of cells at the air-pouch, mitochondrial activity, production of ROS and total proteins production, as well as the number of viable fungi.

Results: *In vitro* experiments showed remarkable direct antifungal activity of PBGR, reducing the number of viable fungi in relation to the original inoculum after 72h of incubation. *Ex vivo* experiments showed that PBGR caused a decrease in the influx of PMNs in relation to non-treated infected controls.
Mitochondrial activity was higher in mice treated with PBGR, that in those of the control group. ROS production was lower in mice treated with PBGR. PBGR was able to reduce the number of viable Pb18 in treated mice.

Conclusions: Our results suggest that PBGR has a direct antifungal effect and is able to prevent fungal growth and also to increase PMNs activation. This data allows us to propose PBGR as a new natural therapeutic alternative to complement PCM treatment.

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