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TITLE

PRELIMINARY EVALUATION OF ANTI-FIBROTIC POTENTIAL OF GREEN PROPOLIS EXTRACT: INHIBITION OF NLRP3 INFLAMMASOME AND MODULATION OF HEPATIC STELLATE CELL IN SCHISTOSOMIASIS MANSONI

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ABSTRACT

Schistosomiasis mansoni is one of the main parasitic diseases affecting public health, characterized by the formation of granulomas and hepatic fibrosis due to the response to parasite eggs trapped in the host tissue. Several studies indicate that soluble egg antigens (SEA) of *Schistosoma mansoni* activate hepatic stellate cells (HSCs), promoting hepatic fibrosis. This process involves the activation of the NLRP3 inflammasome, which results in the synthesis of IL-1 β and IL-18, cytokines that regulate the expression of TGF- β 1 and promote the transition of quiescent HSCs to a myofibroblastic phenotype, increasing collagen production and extracellular matrix. Considering that praziquantel does not reverse this pathogenesis, this study aims to evaluate the potential of a standardized green propolis extract (Pex) to inhibit the activation of the NLRP3 inflammasome and the progression of hepatic fibrosis in murine models of schistosomiasis, positively modulating molecular factors associated with HSC inactivation, and investigating the parasitological and immunological effects associated with the disease. In vitro, GRX cells (cell line obtained by spontaneous migration of cells from granulomas induced in liver of C3H/HeJ mice infected with *Schistosoma mansoni*) demonstrated a cytotoxic concentration (CC50) > 100 μ g/mL (6 h and 12 h) and > 70 μ g/mL (24 h) after treatment with Pex, while LX-2 cells (human hepatic stellate cell line) showed a CC50 > 100 μ g/mL at 24 h and 48 h of incubation. Western blot analyses showed a significant reduction in NLRP3 protein expression in GRX cells that were doubly stimulated for inflammasome activation [1^o signal lipopolysaccharides (LPS) and 2^o signal SEA] subsequently incubated with Pex. Furthermore, qRT-PCR assays showed that Pex reduced the expression of transcription factors associated with HSC activation (NF- κ B, TGF- β 1, and COL1 α 1) in LX-2 cells, while factors associated with HSC inactivation (PPAR γ and GATA) were positively regulated after 24 h and 48 h of incubation. In the in vivo model, treatment with 300 mg/kg of Pex from the 35th to the 42nd day post-infection also showed a significant reduction in NLRP3 protein expression in liver. These preliminary results suggest the potential of Pex to inhibit the formation and activation of the NLRP3 inflammasome, as well as negatively modulate the transcription of molecular factors associated with the progression of hepatic fibrosis and positively modulate factors associated with the regression of this disease.

KEYWORDS

Inflammasome, Hepatic Fibrosis, Hepatic Stellate Cells, NLRP3, *Schistosoma mansoni*.

FINANCIAL SUPPORT

CNPq (308903/2021-8); FAPESP (2024/09101-9)