MODULATION OF INFLAMMATORY RESPONSES BY *SUTHERLANDIA FRUTESCENS*

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ABSTRACT

Sutherlandia frutescens (L.) R. Br (*Lessertia frutescens*) is a medicinal plant traditionally used in southern Africa. It has been used for patients suffering from numerous types of cancer, infectious diseases, and various inflammatory conditions. This study was designed to determine the impact of *S. frutescens* on the inflammatory response and anti-microbial activities on cell and/or animal models. Aqueous and ethanolic extracts of *S. frutescens* were made and verified using HPLC. These extracts were used to treat murine macrophages (e.g., RAW 264.7 cells and primary macrophages isolated from mice) to evaluate the impact of *S. frutescens* on *in vitro* inflammatory responses. This study found that the aqueous extract and a polysaccharide-enriched fraction from the aqueous extract exhibited an immuno-stimulatory activity on murine macrophages. Treatment with aqueous extract or polysaccharides increased the production of reactive oxygen species (ROS), nitric oxide (NO), and inflammatory cytokines/chemokines via activating the toll-like receptor 4 signaling pathway.

On the other hand, the ethanolic extract of *S. frutescens* dose-dependently decreased the production of ROS, NO, inducible nitric oxide synthase (iNOS), and various inflammatory cytokines and chemokines in murine macrophages co-stimulated with lipopolysaccharide (LPS) and interferon gamma (IFN γ). Follow up experiments

demonstrated that the anti-inflammatory activity of the ethanolic extract was mediated via reductions in the activation of NF- κ B, extracellular-signal-regulated kinase 1/2 (ERK1/2), and signal transducers and activators of transcription 1 (STAT1). RNA sequencing provided more evidences to support the anti-inflammatory activity of the ethanolic extract of *S. frutescens*. To our surprise, chlorophylls isolated from *S. frutescens* had a greater effect on the anti-inflammatory of *S. frutescens* than that of unique compounds (i.e., sutherlandiosides and sutherlandins).

To investigate the impact of oral consumption of *S. frutescens* on *in vivo* inflammatory responses and anti-microbial activities, mice were fed with AIN-93G based diet with/without containing ground *S. frutescens* powder or were gavaged with *S. frutescens* extracts followed by challenge with *E. coli* or LPS. These experiments found that oral consumption of *S. frutescens* had limited or no impact on the *in vivo* inflammatory responses and anti-microbial activities.

Overall, this study provide a better understanding on the beneficial therapeutic properties of *S. frutescens* using *in vitro* models, however these studies in a laboratory mouse model suggest that consumption of *S. frutescens* had only a modest impact on host anti-microbial and inflammatory responses to a gram-negative microbial challenge whether intact microbes or bacterial endotoxin (i.e., LPS) was used.