

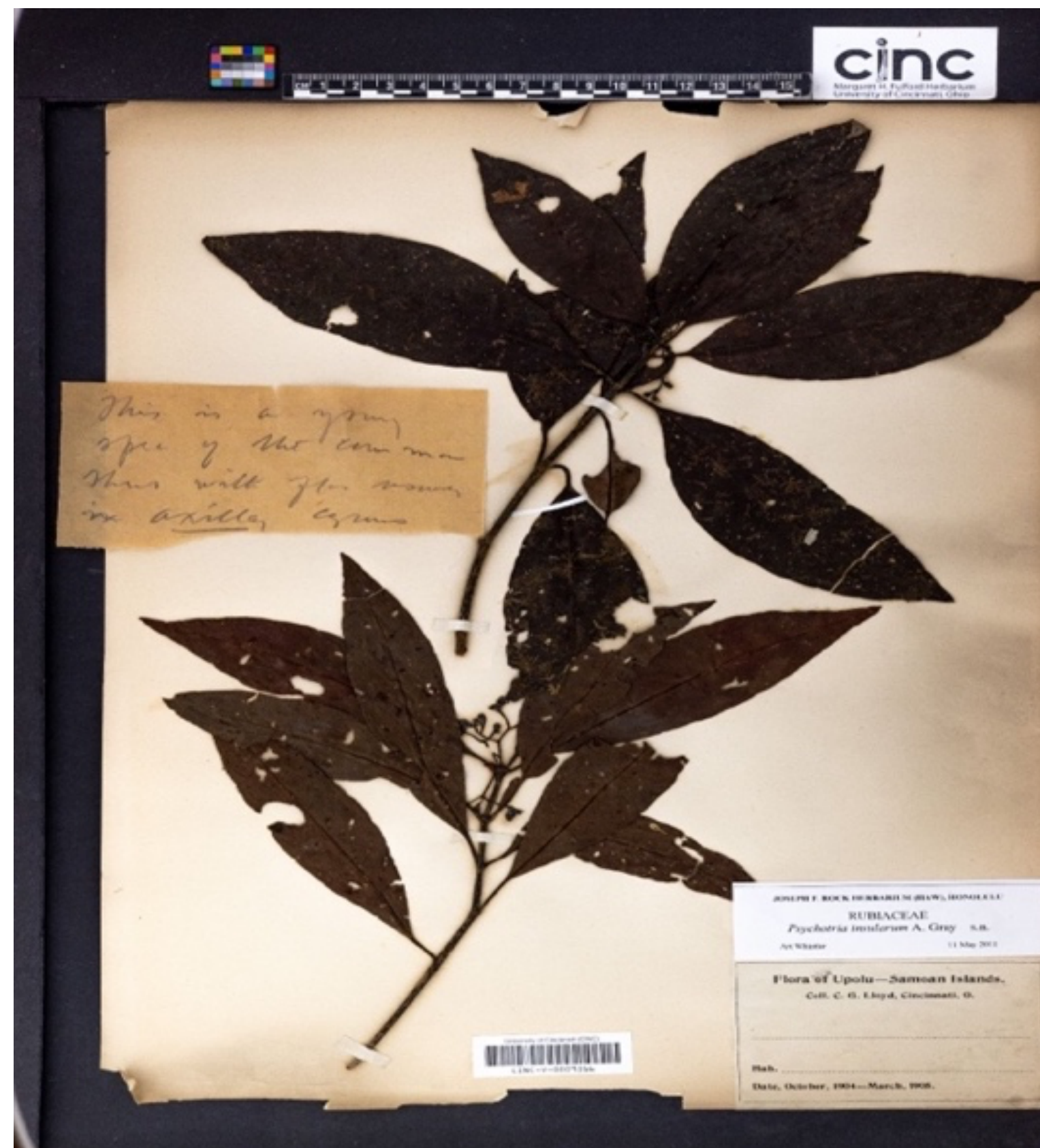
# Traditional *Psychotria insularum* vs. Western Medicine's Ibuprofen: Parallels in Inflammation Reduction via Iron Chelation

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## Introduction

An estimated 80% of the world's population use herbal medicine as a primary source of health care<sup>2</sup>. Many of the active compounds found in plants continue to be used in modern medicine and are major effectors of drug development today. Looking within the *Rubiaceae* family of flowering plants commonly known as coffee family), specifically, species of *Psychotria* are widely distributed throughout the tropics. Cincinnati's Curtis Gates Lloyd, of Cincinnati's Lloyd Brothers Pharmacists, collected *Psychotria* in Samoa from 1904-1905 as part of his comprehensive collection of the Samoan flora<sup>6</sup>. Samoan traditional medicine uses species of *Psychotria* to treat inflammation associated with various conditions<sup>5</sup>. While researching the ethnobotanical uses of the Samoan plant specimens collected by Curtis Gates Lloyd, I became especially interested in *Psychotria insularum*, and the focus of this study was to compare the therapeutic and metabolic similarities between the effects of active compounds in *P. insularum* with modern day Ibuprofen.



**Figure 1.** *P. insularum* collected by Curtis Lloyd Gates, October 1904- March 1905. Identified by Art Whistler, May 11, 2011. Imaged at the University of Cincinnati, Margaret H. Fulford Herbarium.

"Matalafi", the leaf homogenate of *Psychotria insularum*, is habitually used in Samoan traditional medicine to treat inflammation (Figure 1). Matalafi has been shown to have powerful effects on the body comparable to Ibuprofen, which is used today as an anti-inflammatory drug<sup>5</sup>. Through iron chelator activity, both Ibuprofen and *P. insularum* enable treatment of inflammation resulting from iron-overload in the body. Using metabolomics, a deeper understanding of Samoan traditional medicine and its parallels to western medicine can be used for advancement in pharmaceuticals.

## *P. insularum* and Inflammation

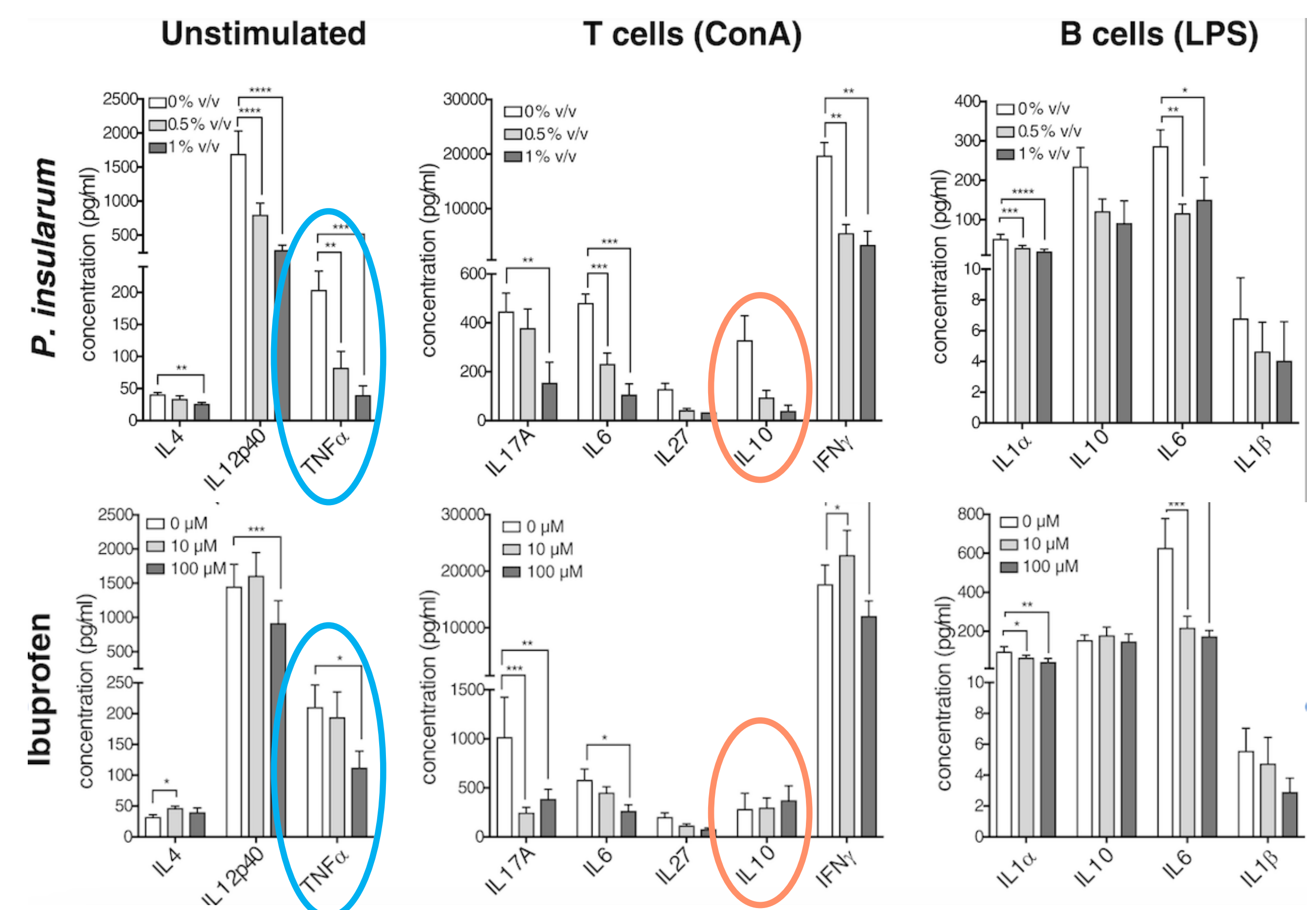
An iron homeostasis role was identified in *P. insularum* by a study published in the *Proceedings of the National Academy of Sciences of the United States of America*, as the mechanism of action in its traditional use for reducing inflammation. Using baker's yeast as a model organism and through fractionalization of the homogenate, the researchers were able to identify two flavanol glycosides, *rutin* and *nicotiflorin*, each which bind iron. Relating these findings to mammalian immune cells and their traditional action in the human body, researchers found that the iron-chelator activity of the *P. insularum* homogenate decreased pro-inflammatory responses in the body and enhanced anti-inflammatory cytokine responses within immune cells. Dysregulated iron homeostasis is associated with progressive inflammation, directly related to the inflammatory response of the body. When iron is present in excess, iron chelation takes place to excrete the excess particles. Thus, the active compounds present in *P. insularum* reduce the iron availability in the body via additional iron chelation<sup>5</sup>.

## Ibuprofen and Iron Chelation

Ibuprofen chelates iron in a stable manner, enabling treatment of inflammation due to iron overload. Ibuprofen has been shown to chelate iron in a stable form, along with suppression of reactive oxygen species within the body. Contributing to inflammation as well is the damage that free radicals in the body cause on cells. Ibuprofen inhibits the generation of free radicals, which contributes to its anti-inflammatory effects<sup>3</sup>. There is evidence that *P. insularum* has similar, if not identical, therapeutic effects as Ibuprofen. *Psychotria insularum* has antioxidant activity as well, in that iron chelation is involved in many antioxidant and anti-inflammatory activities. Plants of the *Psychotria* genus in general are promising sources of antioxidants in that their extracts have numerous observed radical scavenging properties<sup>1</sup>.

## Therapeutic Similarities

Comparing *Psychotria insularum* homogenate with the anti-inflammatory drug ibuprofen, cytokines which highlighted proinflammatory and anti-inflammatory T helper (Th) subsets were analyzed. To investigate adaptive immunity, cytokines were measured in both stimulated and unstimulated splenocytes in the presence of both *P. insularum* and ibuprofen. Results indicated that activated immune cells in the presence of both *P. insularum* and ibuprofen had similar results overall on inflammation (Figure 2).



**Figure 2.** The anti-inflammatory activity of *P. insularum* on activated immune cells. Cytokine production by unstimulated splenocytes shows baseline responses to both *P. insularum* and ibuprofen, Con-A (concanavalin A, a lectin which activates T-cells) stimulated splenocytes, and LPS (lipopolysaccharide) stimulated splenocytes (B-cell activated). X-axis details cytokines that highlighted proinflammatory and anti-inflammatory subsets when in stimulated and unstimulated splenocytes<sup>5</sup>. Similar affects are observed of both *P. insularum* and ibuprofen. \* In unstimulated *P. insularum*, the baseline production of fever-reducing cytokine TNF $\alpha$  was severely reduced compared to unstimulated ibuprofen. \*The *P. insularum* homogenate increased production of anti-inflammatory cytokine IL10, and significantly reduced production of proinflammatory Th1-inducing cytokine IL12p40.

## Further Discussion

The prevalence of chronic wounds is rapidly increasing worldwide and is the third most expensive disorder to treat after cancer and cardiovascular diseases. Various medicinal plants have been used for wound healing and antimicrobial properties, including the Samoan plant species *Peperomia pellucida*, *Physalis angulata*, *Polyscias fruticosa*, and *Dioscorea bulbifera*<sup>6</sup>.

Plants contain complex mixtures of phytochemicals and frequently have multiple therapeutic properties. For instance, ethanol extracts of the Samoan plant *P. insularum* are shown to inhibit the growth of certain strains of *Staphylococcus aureus*. Additionally, Samoan species *Homalanthus nutans*, known as the mamala tree, has been used for treatment of HIV-AIDS. Prostratin, a chemical from the bark of the mamala tree, has in vitro activity against HIV, decreasing the expression of HIV receptors on healthy cells, thereby reducing the rate of infection of healthy cells.

Samoan plant species have been shown to aid in the development of new wound healing agents, but further research needs to be done before implicating these practices into our society<sup>4</sup>. Research on *P. insularum* may be used as protective agents against cancer, diabetes, cardiovascular diseases, neurodegenerative diseases, obesity, and COVID-19. *Rutin*, a component of *P. insularum*, plays a major role in inhibiting the viral replication of the SARS-CoV-2 virus *in vitro*, which can contribute to further investigation using *P. insularum* as possible treatment for COVID-19 and other coronaviruses<sup>5</sup>.

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