Synopsis: TEA study – Tea endemic for atopy

Title
A study to evaluate the efficacy of low and high dose “cup-of-tea” Aspalathus linearis in allergic rhinitis

Site Location
UCT Lung Institute, Cape Town

Background
Aspalathus linearis, commonly known as Rooibos, has been extensively used as an alternate homeopathic remedy for alleviating symptomatology of various diseases and ailments including allergy. It is an indigenous shrub of the Cederberg region in the Western Cape Province of South Africa rich in flavonoids and polyphenols.

In vitro data on the immuno-modulatory and anti-allergic effects of Rooibos are limited to animal models or cell lines [1-3]. A single study, conducted 36 years ago using non-standardised extracts, a single dose, and poor clinical end-points (only skin prick test) suggested no clinical effect of Rooibos tea drinking on allergic inflammation [4]. However, we have in vitro data using standardised extracts of unfermented and fermented Rooibos, and atopic patient basophils and normal human skin-derived mast cells, that show a dose-dependent suppression by both extracts of IgE- and non-IgE mediated basophil activation and mast cell degranulation (see Figures 1 and 2 in June 2018 progress report submitted to SARC). This data provides strong justification to perform clinical study using standardised extracts, a high and low-dosing strategy, and robust clinical end-points in atopic patients.

Primary and Secondary study objective(s)
The primary objective is to assess whether five days of drinking a standardised Rooibos tea extract (at low or high “cup-of-tea” dosing) can reduce provoked allergic rhinitis symptoms, as measured by Total Nasal Symptom Score (TNSS) and peak inspiratory nasal flow (PINF) after a house dust mite nasal allergen challenge (NAC).

The secondary objective is to assess whether five days of drinking a standardised Rooibos tea extract (at low or high “cup-of-tea” dosing) can reduce ex vivo basophil activation with house dust mite, as measured by percentage positive CD63 basophils using flow cytometry, as well as sulfidoleukotrienes release using an ELISA.

The third objective is to assess whether whether five days of drinking a standardised Rooibos tea extract (at low or high “cup-of-tea” dosing) can reduce the allergic wheal size (in mm) during in vivo house dust mite skin prick testing.

Study design
This is a two phase study design with a go/no-go decision point after the dose-finding phase.
Phase 1. (see figure 1A for outline)

This is a open-labelled, parallel group, cross-over two-arm study of five days of drinking a standardised Rooibos tea extract (at low or high “cup-of-tea” dosing) in adult subjects with a proven allergic rhinitis symptoms and specific IgE > 10 IU/l to either/both of *dermatophagoides farinae* or *pteronyssinus*. The dosing in the two arms will be:

1. Standardised extract of Rooibos tea (2 cups/day for 5 days followed by 6 cups/day for 5 days) – unfermented or fermented extract is still to be decided
2. Standardised extract of Rooibos tea (6 cups/day for 5 days followed by 2 cups/day for 5 days)

Phase 2 (see Figure 1B)

If the go/no-go decision criteria are met, the phase 2 study will continue. This will be a double-blind, placebo controlled randomised controlled study using one selected during phase 1

**Study duration**

Phase 1 of the study will be 16 days including 4 days pre-treatment, 2 x 5 days of treatment and 2 days of washout in between. Phase 2 of the study would only be 9 days including 4 days pre-treatment, and a 5 day treatment period.

**Population**

Adult > 18 years subjects with history suggestive of house dust mite triggered allergic rhinitis and confirmed specific IgE > 10 IU/l to either/both of *dermatophagoides farinae* or *pteronyssinus*.

**Sample size**

Phase 1: 10 subjects will be sufficient to determine if there is any measurable difference(s) between pre- and post-Rooibos treatment nasal allergen challenge to house dust mite.

Phase 2: Enrolling 25 subjects per group, the study will is estimated to have >90% power to detect a minimally clinically important difference for TNSS of 1.5 units between treatment groups (standard deviation of 1.5). The significance level is set to 2-sided, 0.05 level.

**Treatments**

**Study treatment**

Standardised Rooibos tea extract prepared by Prof L Joubert. We will still determine the use of a unfermented or fermented tea preparation. Preparation will be strictly controlled, involving 200ml hot water + 3g of extract with infusion time of 2 minutes.

**Dose/Route/Schedule**

Phase 1 (Phase 2 dosing schedule to be selected as either group 1 or 2 below)

*Group 1*: 2 cups/day (total volume 400mls) for 5 days followed by 6 cups/day (1200mls) for 5 days with 2 days washout in between

*Group 2*: 6 cups/day for 5 days followed by 2 cups/day for 5 days with 2 days washout in between

We are aware that there is a aspalathin-enriched nutraceutical under development by researcher at the SA Medical Research Council (PI: Prof Johan Louw); but think that it will
be preferrable to use a standardised extract with a cup-of-tea dosing. The justification for this approach includes: i) allow us to answer the question of whether an allergic rhinitis patient can drink sufficient already available Rooibos tea to impact their disease, ii) we do not think that aspalathin, the Rooibos extract component enriched in the nutraceutical with well established anti-diabetic and anti-cancer properties [5, 6], is the most important component responsible for the anti-allergic properties; iii) the development of this GMP-quality product is still at the safety trial (phase IIa) stage, therefore not currently allowing for a efficacy clinical trial at this stage.

Endpoint(s)

Primary

The primary endpoint is the difference in pre- and post-treatment TNSS at 10 minutes following the single-dose nasal allergen challenge (NAC).

Secondary

The difference between the area under the curve for 12 hours following NAC (AUC12) for nasal symptoms score and Peak Nasal Inspiratory Flow (PINF) pre- and post-treatment

The difference in Peak Nasal inspiratory flow (PNIF) at 10 minutes pre- and post-treatment

Change in the number of positive CD63 basophils from pre- and post-treatment

Change in the sulfidoleukotrienes release by basophils from pre- and post-treatment

Change in the response to skin prick test from from pre- and post-treatment

Nasal allergen challenge

Nasal allergen challenge is both a useful clinical tool and a well-established method to characterise nasal symptoms and obstruction in direct response to an offending allergen. It has been widely used in immunotherapy trials for a number of years and is performed safely at the UCT Allergy and Immunology clinic. Briefly, subjects are aclimitised in a room with stable temperature and humidity. Thereafter, a standardised dose of allergen (in this case house dust mite) is delivered via a nasal dispenser into each nostril. At 5 minute intervals nasal symptoms scores are collected. Total nasal symptoms score (TNSS), is determined as the sum of individual scores for “sneezing”, “itching”, “nasal blockage” “runny nose” on a 4 point Likert scale with 0 representing no symptoms and 3 representing maximum symptoms. The mean of three peak nasal inspiratory flow (PNIF) measures will be obtained using an In-check™ flow meter (Clement Clarke International Ltd, Harlow, UK).
Figure 1A and B Schematic of study design

Fig.1A: Phase 1

Group 1 (5 patients):
- Off any treatment
- Rooibos tea (2 cups/day)
- Washout
- Rooibos tea (6 cups/day)

Tests:
- Nasal challenge
- Blood collection for basophil activation (Flow CAST + CAST ELISA) + skin-prick test

Rooibos tea preparation:
1 cup = 200ml water + 3g tea

Fig.1B: Phase 2

Group 1 (25 patients):
- Off any treatment
- Rooibos tea

Tests:
- Nasal challenge
- Blood collection for basophil activation (Flow CAST + CAST ELISA) + skin-prick test

Group 2 (25 patients):
- Off any treatment
- Placebo
References


