Safety of *Sutherlandia fructescens* in HIV-seropositive South African adults: an adaptive double-blind randomized placebo controlled trial

Douglas Wilson,[1] Kathleen Goggin,[2] Karen Williams,[2] Mary Gerkovich,[2] Nceba Gqaleni,[1] James Syce,[3] Patricia Bartman,[4] Quinton Johnson,[5] William Folk[6]

[1] University of KwaZulu-Natal, [2] University of Missouri–Kansas City, [3] University of the Western Cape, [4] Edendale Hospital Research Unit, [5] The International Centre for Indigenous Phytotherapy Studies, [6] University of Missouri-Columbia

Background

- Medicinal plants are widely prescribed by Traditional Health Practitioners in South Africa

- Phytotherapies containing *Sutherlandia fructescens* (Unwele, Sutherlandia) is used to treat many conditions including symptoms arising from HIV infection
  - Stress, loss of appetite, quality of life

- The safety and efficacy of *S. fructescens* in HIV seropositive adults is unknown

- *S. fructescens* did not produce toxicity
  - In vervet monkeys to a dose of 80mg/kg over 3 months
  - In healthy adults at a dose of 400 mg twice daily

Objectives

Primary Objectives:

- To determine the safety of *Lessertia frutescens* when used by HIV-1 infected adults with early disease
- To document the impact of *Lessertia frutescens* on the number, nature and duration of self-reported infections in HIV-infected adults with early disease

Secondary Objectives:

- To determine the effect of *Lessertia frutescens* on quality of life indices in HIV-infected adults measured by the Medical Outcomes Study HIV Health Survey (MOS-HIV) (secondary outcome)

Tertiary Objective

- To document the impact of *Lessertia frutescens* on markers of HIV disease progression

Methodology

- Single centre double-blind randomized placebo control trial
  - Department of Medicine, Edendale Hospital

- Two Stages:
  - Stage 1 – placebo vs. 400 mg or 800 mg or 1,200 mg twice daily
  - Stage 2 – placebo vs. safest dose selected from Stage 1

- Sutherlandia 400 mg capsules and matching placebo produced in accordance with Good Manufacturing Practise
  - Additional guidance from the NIH and MCC

- Safety monitoring set at pharmaceutical industry standards
  - Independent study monitor
  - Oversight from an independent Data Safety Monitoring Board

Methodology continued

- Adherence supported with pill boxes, capsule counts, random telephone calls

- Outcomes determined by evaluating
  - Adverse events (including DAIDS grading)
  - Infection events
  - Serial responses to standardized questionnaires translated into isiZulu
  - CD4 count and HIV viral load

Inclusion criteria

1. Age ≥21 years and <65 years
2. HIV-1 infection documented in the medical record by two different rapid tests for HIV-1 antibodies
3. CD4 count >350 cells/µL
4. Viral load ≥1,000 copies/mL
5. Normal haematological function (haemoglobin >10.0 g/dL, absolute neutrophil count >1.0x109, eosinophil count <2.4x109, platelet count >100x1011)
6. Absence of clinically significant renal disease: 1. serum creatinine <140 µmol/L; 2. glomerular filtration rate ≥ 60 mL/min calculated using the formula of Cockroft and Gault and 3. absence of haematuria and/or ≥1+ proteinuria on urine dipstick.
7. Normal liver function (INR <1.5, bilirubin <1.5x normal, ALT <2x normal, ALP <2x normal)
8. Random glucose <11.1 mmol/L
9. Normal electrocardiogram
10. Attendance at the Primary Care clinic for at least 2 visits before screening
11. Cognitive capacity sufficient to provide informed consent
12. Has not taken traditional medication for 28 days prior to screening

Exclusion criteria

1. Any AIDS-defining diagnosis
2. Weight loss >5% of body weight within the preceding six months
3. Other features of undiagnosed tuberculosis (including cough, unusual fatigue, drenching night sweats and abnormal chest radiograph).
4. Any other significant disease (for example active tuberculosis, hypertension, diabetes mellitus and other endocrine disorders, peptic ulcer disease, gastrointestinal malabsorption, psychiatric illness) either newly diagnosed or controlled by medication.
5. Use of any allopathic medication other than isoniazid for tuberculosis prophylaxis
6. Use of traditional medicines within the past 28 days
7. Prior or current use of antiretroviral therapy
8. History of allergic conditions (e.g. asthma, eczema, urticaria requiring medical therapy on more than one occasion) or drug allergy/hypersensitivity.
9. Either history or family history of autoimmune disease (e.g. systemic lupus erythmatosis, Guillian Barre, haemolytic anaemia)
10. Alcohol use of >7 units per week or 3 units per occasion, tobacco use of more than 10 cigarettes per day or description of recreational drug use within the past 6 months
11. Pregnancy or breast-feeding
12. Women of childbearing potential who are sexually active and not using medically accepted dual contraceptive measures, as judged by the investigator.
13. Participation in a clinical study of any investigational product 1 month prior to the screening visit.

Week 1 / Baseline	**Week 24**	**INTERIM ANALYSIS**	**Week 24**	**TOTAL**
Placebo	12	Continue Stage 2 Safety: Study Termination	36	48
400 mg bid L Sutherlandia	12		36	48
800 mg bid L Sutherlandia	12			
1200 mg bid L Sutherlandia	12			
TOTAL	48*	TOTAL	72	120*

*1 additional participant enrolled for every 6 – compensate for anticipated loss to follow up

Methodology continued – adaptive components

After completion of Stage 1 and interim analysis:

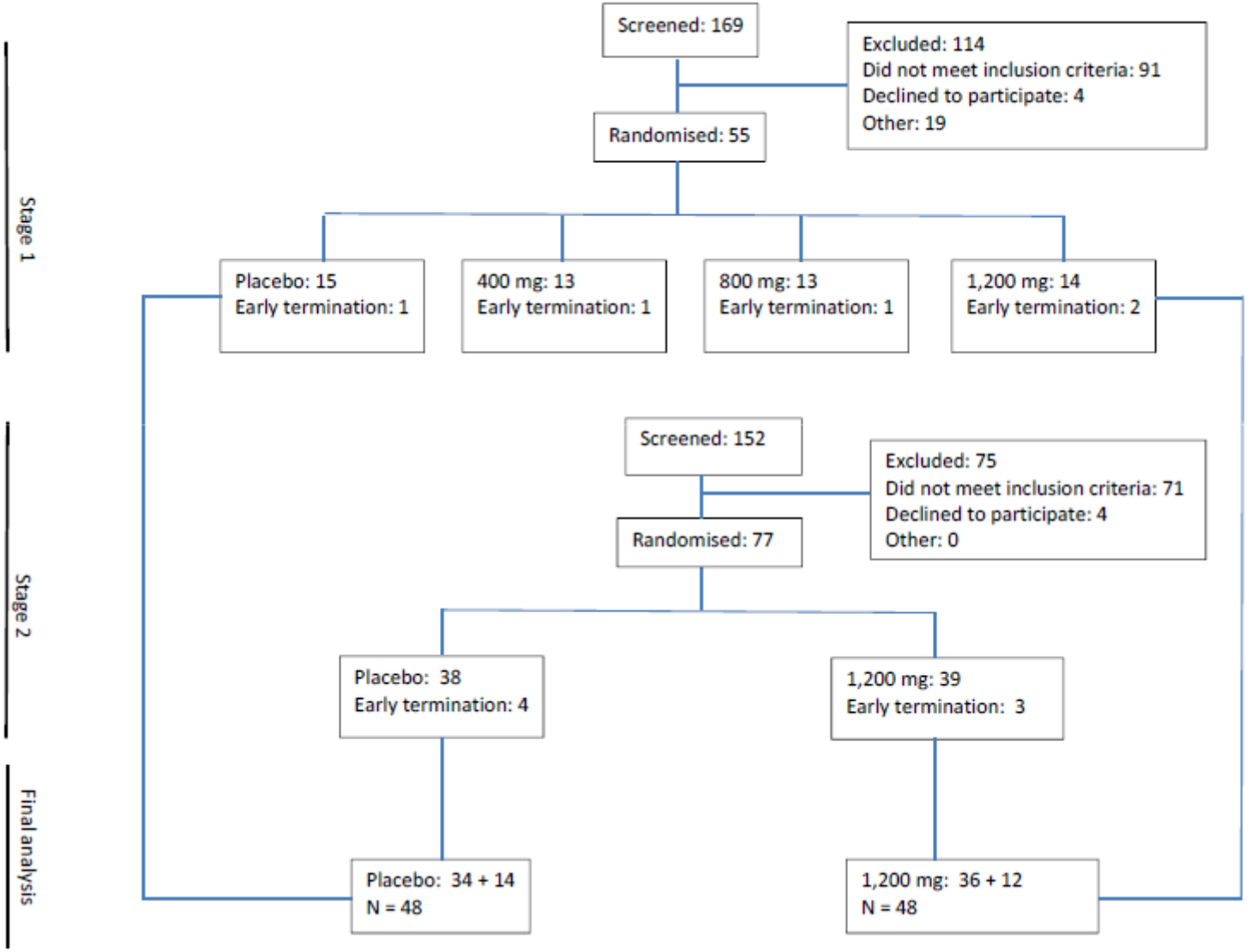
- Burden of infection (defined as duration of infection in days) identified as an important variable
  - Start and stop dates recorded for adverse event reporting used to define duration
  - In Stage 2 participants with encouraged to report infection events at time of onset and telephoned every two days to determine stop date
  - Case definitions derived from DoH Primary Care Essential Drug List
  - Stage 1 adverse event source data coded independently by two clinicians

- 1,200 mg dose selected for Stage 2 after reviewing all safety and preliminary efficacy data from Stage 1

Regulatory oversight

- Biomedical Research Ethics Committee, University of KwaZulu-Natal
- South African Medicines Control Council
- KwaZulu-Natal Department of Health
- Data Safety Monitoring Board, University of Cape Town

Results: CONSORT diagram



Baseline characteristics

Characteristic	Sutherlandia arm	Placebo arm
Gender Female	79%	81%
	Mean (SD)	Mean (SD)
Age years	32.8 (8.5)	32.7 (8.3)
Education (Grade)	10.5 (2.7)	10.2 (2.6)
Viral load (Log) cpm	4.09 (0.60)	4.06 (0.63)
CD4 count cells/µL	520.9 (143.5)	536.4 (135.5)
Haemoglobin g/dL	12.8 (1.1)	12.9 (1.3)
Albumin g/L	40.4 (3.5)	40.9 (3.6)
MCV fL	88.9 (3.6)	88.9 (5.1)
Neutrophils %	50.5 (9.8)	50.6 (10.2)
Triglycerides mmol/L	0.9 (0.4)	0.9 (0.4)
Total cholesterol mmol/L	3.6 (0.9)	3.9 (0.9)
Sodium mmol/L	136.6 (2.3)	136.5 (2.5)
Urea mmol/L	3.4 (1.0)	3.7 (1.2)
ALT µkat/L	21.7 (18.7)	19.3 (9.3)
Bilirubin mmol/L	6.8 (3.1)	6.9 (3.7)

P > 0.2 for all comparisons

Results continued

- No serious adverse events occurred
- Number of adverse events similar in the two arms

Biochemical parameter trends

Parameter	Baseline Mean (SD)	Week 12 Mean (SD)	Week 24 Mean (SD)	P value Time	P value Interaction
Urea mmol/L				0.451	0.518
Sutherlandia	3.4 (1.0)	3.5 (1.1)	3.7 (1.1)		
Placebo	3.7 (1.2)	3.6 (1.3)	3.8 (1.1)		
Sodium mmol/L				0.226	0.215
Sutherlandia	136 (2)	136 (2)	136 (3)		
Placebo	136 (2)	136 (2)	137 (2)		
Bicarbonate mmol/L				0.961	0.926
Sutherlandia	25 (2)	25 (3)	26 (3)		
Placebo	25 (3)	25 (2)	26 (3)		
Alanine aminotransferase				0.911	0.932
Sutherlandia	22 (19)	23 (21)	23 (21)		
Placebo	19 (9)	23 (19)	20 (13)		
Alkaline phosphatase µkat/L				0.569	0.572
Sutherlandia	66 (20)	67 (35)	67 (25)		
Placebo	67 (19)	67 (18)	67 (19)		
Total bilirubin µmol/L				0.816	0.817
Sutherlandia	7 (3)	6 (2)	7 (4)		
Placebo	7 (4)	7 (3)	7 (4)		
Albumin g/L				0.657	0.636
Sutherlandia	40 (3)	40 (3)	40 (3)		
Placebo	41 (4)	40 (4)	41 (3)		
Random glucose mmol/L				0.05	0.055
Sutherlandia	4.5 (0.6)	5.0 (1.0)	4.8 (0.7)		
Placebo	4.7 (0.8)	5.0 (0.9)	4.5 (0.7)		

Haematological parameter trends

Parameter	Baseline Mean (SD)	Week 12 Mean (SD)	Week 24 Mean (SD)	P Value Time	P Value Interaction
Hemoglobin g/dL				0.07	0.981
Sutherlandia	12.8 (1.1)	12.8 (1.3)	12.7 (1.3)		
Placebo	12.8 (1.2)	13.8 (1.3)	13.2 (1.3)		
Platelets ×109/L				0.581	0.787
Sutherlandia	296 (78)	289 (68)	288 (64)		
Placebo	285 (60)	292 (78)	285 (71)		
Leucocyte count ×109/L				0.001	0.98
Sutherlandia	5.7 (1.7)	5.4 (1.5)	5.2 (1.4)		
Placebo	5.6 (1.7)	5.3 (1.3)	5.3 (1.5)		
Lymphocyte count ×109/L				0.001	0.96
Sutherlandia	2.1 (0.7)	2.0 (0.6)	2.0 (0.6)		
Placebo	2.1 (0.6)	2.0 (0.5)	1.9 (0.6)		
Neutrophil count ×109/L				0.011	0.922
Sutherlandia	3.0 (1.3)	2.8 (1.1)	2.6 (01.0)		
Placebo	2.9 (1.3)	2.7 (1.0)	2.7 (1.2)		
Eosinophil count ×109/L				0.019	0.672
Sutherlandia	0.18 (0.16)	0.21 (0.20)	0.24 (0.22)		
Placebo	0.18 (0.15)	0.18 (0.13)	0.20 (0.17)		
Monocyte count ×109/L				0.001	0.31
Sutherlandia	0.32 (0.13)	0.30 (0.11)	0.29 (0.10)		
Placebo	0.28 (0.08)	0.30 (0.08)	0.28 (0.08)		

HIV related parameter trends

HIV Measures	Baseline Mean (SD)	Week 12 Mean (SD)	Week 24 Mean (SD)	P value Time	P value Interaction
CD4					0.869
Sutherlandia	521 (143)	499 (177)	476 (156)	0.028	
Placebo	536 (135)	532 (168)	517 (186)	0.193	
Viral Load log cpm					0.347
Sutherlandia	4.09 (0.60)	4.03 (0.65)	3.89 (0.74)	0.036	
Placebo	4.06 (0.63)	3.84 (0.79)	3.87 (0.69)	0.046	
BMI					0.393
Sutherlandia	28.0 (5.0)	28.3 (4.9)	28.4 (4.9)		
Placebo	29.3 (6.3)	29.5 (6.2)	29.4 (6.2)		

Impact on burden of infection

Infections	Placebo	Sutherlandia	P Value
Number of Infections			0.372
None	22 (42.3%)	17 (33.3%)	
One	17 (32.7%)	18 (35.3%)	
Two	8 (15.4%)	10 (19.6%)	
Three	3 (5.8%)	3 (5.9%)	
Four	2 (3.8%)	3 (5.9%)	
Type of Infection			0.784
Viral	26 (51.0%)	33 (53.2%)	
Bacterial	18 (35.3%)	24 (38.7%)	
Fungal	5 (9.8%)	4 (6.5%)	
Protozoal	2 (3.9%)	1 (1.6%)	
Burden of Infection			
Mean BOI days	5.0 (5.5)	15.4 (30.1)	0.022
Total BOI¥ days	9.0 (12.7)	29.0 (66.0)	0.033
Mean BOI days	5.0 (5.5)	9.0 (12.7)	0.045
Total BOI¥ days	9.0 (12.7)	18.2 (25.4)	0.065

BOI: Burden of infection; ¥ exclusion of outliers

Impact on qualitative measures of health: Medical Outcomes Score (MOS) subscales

Measure	Placebo	Sutherlandia	P Value Group	P Value Time
Pain			0.22	0.227
Baseline	78.0 (24.7)	81.3 (18.8)		
Week 4	79.5 (21.6)	80.7 (20.3)		
Week 12	74.8 (20.3)	78.2 (22.4)		
Week 24	74.3 (21.3)	81.9 (20.2)		
Health Distress			0.956	0.055
Baseline	67.9 (24.9)	71.6 (18.9)		
Week 4	75.9 (20.8)	71.4 (20.2)		
Week 12	73.3 (22.5)	73.1 (19.9)		
Week 24	71.4 (20.3)	73.5 (21.7)		
Cognitive Function			0.74	0.228
Baseline	67.5 (27.6)	69.3 (19.1)		
Week 4	70.5 (22.5)	66.3 (19.1)		
Week 12	69.8 (21.2)	67.8 (23.2)		
Week 24	71.4 (20.3)	70.2 (20.0)		

Internal consistency alpha score >0.7

MOS Quality of Life

Measure	Placebo	Sutherlandia	P Value Group	P Value Time
QOL			0.933	0.03
Baseline	73.6 (24.5)	72.1 (23.3)		
Week 4	75.0 (25.5)	76.4 (22.9)		
Week 12	73.5 (25.2)	77.4 (22.6)		
Week 24	82.2 (18.2)	78.1 (24.8)		

Center for Epidemiologic Studies Depression Scale

Measure	Placebo	Sutherlandia	P Value Group	P Value Time
CESD Mean (SD)			0.797	0.816
Baseline	13.9 (9.2)	15.5 (8.7)		
Week 4				
Week 12	13.8 (8.0)	14.6 (8.8)		
Week 24	14.1 (10.1)	14.7 (9.2)		
CESD > 16			0.835	0.383
Baseline	35.20%	42.30%		
Week 12	34.70%	43.30%		
Week 24	33.30%	32.70%		

Discussion

- First study to rigorously evaluate the safety of an African traditional phytotherapy in adults living with HIV
  - In early infection
  - Before initiation of antiretroviral therapy
- No evidence for toxicity over 24 weeks
- Trend towards higher burden of infection in the Sutherlandia arm, *without* more infections
  - Observation needs further evaluation
- Reduction in viral load and improved QoL seen in both arms
  - Objective benefit from being in care

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Gary Maartens

Siyabonga Baba Shange