

Sutherlandia frutescens: The meeting of science and traditional knowledge

Oluwaseyi M. Aboyade, Gustav Styger, Diana Gibson and Gail Hughes



FIG. 1. *Sutherlandia frutescens*, showing seedpods and flowers. Photo courtesy of Dr. Merlin Willcox (November 3, 2011).

Introduction

Sutherlandia frutescens (L.) R.Br. (syn. *Lessertia frutescens* (L.) Goldblatt and J.C. Manning) is an indigenous medicinal plant extensively used in South Africa to treat a variety of health conditions. It is a fairly widespread, drought-resistant plant that grows in the Western, Eastern, and Northern Cape provinces and some areas of KwaZulu-Natal, varying in its chemical and genetic makeup across these geographic areas.¹ *Sutherlandia* is widely used as a traditional medicine. Extensive scientific studies are being carried out on the safety, quality, and the efficacy of this medicinal plant to validate the traditional claims, elucidate the bioactive constituents, and conduct clinical trials. This has resulted in a unique situation in South Africa's history, where traditional knowledge and science intersect to provide insight into this popular plant. This photoessay attempts to illustrate the interlinkage of science with the indigenous knowledge of traditional healers, the local knowledge of people who care for the sick, product development, and innovation agenda of the country as it relates to this plant. The essay shows how *S. frutescens*, as a medicinal plant, and the study of its pharmacologic components are represented and understood differently, yet with a similar aim: to enhance its safety. The essay explores the plant as

botanical entity, its local uses and therapeutic properties, and the science related to ongoing phase IIa and IIb clinical trials.



FIG. 2. Flowering *Sutherlandia frutescens*. Photo courtesy of Dr. Merlin Willcox (November 3, 2011).

The Botanical Entity

The Cape Floristic Region (one of the richest areas for plants in the world) is home to *Sutherlandia frutescens*. Specifically, *Sutherlandia* is found in the Fynbos Biome, home to the largest variety of plant species. *S. frutescens* belongs to the class *Magnoliopsida*, order *Fabales*, genus *Sutherlandia*, and species *frutescens*. It was recently proposed that *S. frutescens* be transferred to the genus *Lessertia* D.C. on the basis of the assumption that *Sutherlandia* represents an adaptation to bird pollination. However, this proposed reclassification is contentious, requiring more morphological and genetic evidence.¹

S. frutescens is a medium-sized shrub, with fine grayish-green leaves and red, butterfly-shaped flowers. Its seedpods are large and balloon-like with a slightly reddish tint (Figs. 1 and 2). It is a medicinal plant, mostly harvested wild, but it is also grown in community gardens and commercially on a small number of farms. The plant has more than 25 recorded names. Some are related to the color and shape of the plant's flowers, such as kalkoenbos (turkey bush), hoenderbelletjie (the wattle of a cockerel), eendjie (duckling); to its seedpods, such as blaasbossie (for its balloon-like pods) and blaas-ertjie (balloon-like pea); or to the appearance (unwele [hair]) or taste (bitterbos [bitter bush]) of its downy leaves. Many of its names also refer to medicinal use, such as kankerbos (cancer bush; Afrikaans), insiswa

(dispels darkness; Zulu), phetola (to change; Tswana), and lerumo lamadi (spear of the blood; North Sotho).

The Traditional Uses of *Sutherlandia*

In South Africa, *Sutherlandia* is used by an array of healers, such as herbalists (*inyanga*) (Fig. 3), diviners (*isangoma*), bush doctors (*bossiedokters*), Rastafarians, alternative and allopathic medicine practitioners, and lay people.^{2–6} *S. frutescens* has long been used as a garden plant for flower arrangements, but this bitter-tasting plant is best known for its medicinal values. First records about its use came from Dutch colonists in the Cape, who probably came to know it through interaction with the local San and Khoi.³ The original inhabitants of the Cape, the Khoi San and Nama people, used decoctions made from *Sutherlandia* to wash wounds and to bring down fevers.⁷ Not surprisingly, *S. frutescens* is today still one of the most commonly used medicinal plants in the Western Cape.⁸ It is also sold in *muthi* (medicine) markets and in *amayeza* (medicine) shops in other parts of the country.

Preparation and Use

The aerial parts of the plant (stems, leaves, flowers, and pods), the roots, or only the leaves are usually used to make the infusions and decoctions. A decoction of *Sutherlandia* is used to wash wounds and the eyes and to reduce fevers,⁷ and the infusions from the leaves and stems are used to treat cancers, fever, diabetes, kidney and liver problems, rheumatism, and stomach ailments.⁹ The plant is also used for a diversity of symptoms and conditions, such as depression and stress; as a tonic; to purify the blood and wounds; to treat skin conditions and inflammation; to enhance appetite and prevent wasting; as an emetic; and to treat influenza, hemorrhoids, urinary tract infections, back pain, and gonorrhoea.¹

Traditional healers prepare the decoctions according to the type of disease indicated by the patient. Their preparation ranges from using the leaves, flowers, stems, and roots for different ailments.¹⁰ The traditional healers collect fresh plant materials, dry them, and then stamp or mash them into powder between two stones (Figs. 4 and 5). The preparation is then usually infused in hot or boiling water, left to cool, and given to the sick person.

Currently, *Sutherlandia* is available in various dosage forms, such as capsules and tablets (containing *Sutherlandia* raw material in powdered form), gels for topical application, creams, liquid extracts, and ointments and is found in pharmacies and herbal shops.¹ Commercial *Sutherlandia* tablets gained popularity as an herbal product for the treatment of muscle-wasting effects in patients with HIV/AIDS because of a marked improvement in quality of life.^{1,8} To meet the demand for this important medicinal plant, several commercial farms exist in South Africa.



FIG. 3. *Inyanga* in Strand, Western Cape, with fresh plant.



FIG. 4. Dried *Sutherlandia frutescens* plant material ground between stones.



FIG. 5. *Sangoma* preparing dried *Sutherlandia* stems and leaves.

Pharmacology of *Sutherlandia frutescens*

The therapeutic properties of *Sutherlandia* are based on its ability to help the human body to mobilize its own immunologic and physiologic resources to help combat diseases and fight mental and emotional stress.¹¹ Several reviews have been published on the pharmacologic activities of *S. frutescens*.^{1,8,12} *In vitro* and *in vivo* studies carried out on the leaf and whole plant extracts have provided evidence of its antiproliferative, antiviral, antistress, antidiabetic, anti-inflammatory, antimutagenic, antibacterial, antioxidant, and antithrombotic properties, thus validating the traditional claims.¹

Cancer

With regard to the anticancer activity of *Sutherlandia*, studies on the effect of the aqueous extract on cell number, morphology, cell cycle progression, and cell death using MCF-7 (human breast adenocarcinoma) and MCF-12A (human nontumorigenic epithelial mammary gland cells) have been carried out.¹³ A dose-dependent decrease in malignant cell number compared with control and a difference in the mechanism of action of *Sutherlandia* extract on MCF-7 cells compared with MCF-12A cells was observed. The nephrotoxic and apoptotic effect of *Sutherlandia* on kidney cell lines (LLC-PK₁, proximal convoluted tubule epithelium; MDBK, distal convoluted tubule epithelium) revealed that at concentrations higher than 6 mg/ml, the aqueous extract of *S. frutescens* were not cytotoxic and the extract possessed the potential to increase oxidative stress, promote apoptosis, and alter the integrity of mitochondrial membranes in the renal tubules.¹⁴

Stress

A study on the chronic intermittent immobilization stress in adult male Wistar rats fed with aqueous extract of *Sutherlandia* for 28 days showed a reduction in the corticosterone response to chronic stress.¹⁵ Extracts of *Sutherlandia* have also been found to inhibit cytochrome P450, which catalyzes the synthesis of cortisol and its precursors.¹¹ Also, daily treatment with *Sutherlandia* decreased markers of muscle atrophy and inhibited apoptosis in chronic restrained stressed rat models.¹⁶ These studies demonstrated the indigenous use of *Sutherlandia* as a stress-relieving medicinal plant.

Neurologic diseases

Sutherlandia also acts as an antidepressant; as a natural treatment for children with convulsions and epilepsy;¹⁷ and as a supportive treatment for mental and emotional stress, including anxiety.¹⁷

Diabetes

The antidiabetic effects of *Sutherlandia* were observed in animal studies.^{18,19} *Sutherlandia* normalized insulin levels and glucose uptake in peripheral tissues and suppressed intestinal glucose uptake, with no weight gain, in treated rats.¹⁸ Antidiabetic action of *Sutherlandia* in rats with streptozotocin-induced diabetes showed the ability of this plant to induce significant hypoglycemic effect in streptozotocin-treated rats.¹⁹ The diabetic rats treated with *Sutherlandia* maintained their reduced blood glucose levels longer than did their chlorpropamide-treated counterparts.¹⁹ Antioxidant activity was demonstrated by the reduction of free radicals, and suppression of lipopolysaccharides stimulated nitric oxide production.²⁰ In this manner, *Sutherlandia* might also play a role in combating autoimmune diabetes by inhibiting the production of nitric oxide and subsequent damage to the pancreatic β cells.²⁰

HIV

A study showed that the aqueous extract of *Sutherlandia* leaf stimulated reverse transcriptase activity in the presence of tannin, whereas no activity was recorded for the HIV-2 protease. In contrast, the inhibitory effect of various extracts of *Sutherlandia* against HIV-1 reverse transcriptase and^{22,23} integrase exhibited little or no activity.

Chemical Composition

The mechanism of action of *S. frutescens* for these disease and conditions is not known, but several attempts are being made to understand how this plant works. Various chemical compounds that might be responsible for the activity of *Sutherlandia* have been isolated. These include triterpenoids, saponins, flavonoids, γ -aminobutyric acid (GABA) and pinitol.¹ The latter compound may be responsible for the antidiabetic effects and the reversal of muscle-wasting effects in HIV patients, as it has been found to possess insulin-like properties.²⁴ Pinitol also stimulates glucose uptake as well as translocation of the glucose

transporter 4 (GLUT4) to the plasma membrane²⁵ and protects against liver damage and hepatotoxicity induced by d-galactosamine (a model system for hepatitis).²⁶

l-canavanine (2-amino-4-guanidinooxybutyric acid) is the most important nonprotein amino acid found in the leaves of *Sutherlandia*. l-canavanine is a structural analogue of l-arginine and a natural insecticide. Its close similarity to arginine means it can interfere with arginine metabolism and be incorporated into proteins, leading to the formation of dysfunctional proteins.²⁷ Canavanine has also been reported to be a potent anticancer agent,^{28,29} as well as having anti-viral activity against influenza and retroviruses.³⁰ Recent reports also showed that canavanine was a potent inhibitor of nitric oxide synthase and could be useful in the treatment of septic or endotoxic shock.^{31,32} Significant amounts of GABA have also been found in *Sutherlandia*. This compound is an inhibitory neurotransmitter and could explain the use of *Sutherlandia* for the treatment of stress and anxiety.¹

Other chemical compounds, such as cycloartane glycosides³³ and flavonol glycosides,³⁴ have recently been isolated from *Sutherlandia*, which may play a role in the bioactivity of this herbal medicine. Figure 6 shows a chemical profile of the flavonoid constituents of dried *S. frutescens*. Flavonoids have many health-protecting effects, including anticancer and antiviral³⁵ and antiosteoporotic and anticardiovascular activities³⁶ and anti-inflammatory and antiallergic,³⁷ antimicrobial, antiproliferative, chemoprotective, and antioxidant³⁸ effects, that may explain or support the traditional claims of *S. frutescens*. However, none of the above-mentioned chemical constituents of this plant have been conclusively linked to its therapeutic effect, validating the suggestion that the medicinal potential of *Sutherlandia* might be as a result of the synergism between the compounds found in the plant.²⁰

In the last few years, most of the research carried out on *S. frutescens* has been aimed at *in vitro* propagation methods as a tool to meet the commercial demands for this important indigenous medicinal plant. Researchers have focused on an efficient *in vitro* plant regeneration system in order to conserve biodiversity. To this effect, several studies have been undertaken on the molecular and genetic modifications of *Sutherlandia* to regulate and maximize the yield of its bioactive constituents.^{39–42}

Safety of *Sutherlandia*

No serious adverse effects have been reported since ancient times. However, symptoms such as occasional dry mouth, loose stools, or mild diuresis and slight dizziness have been observed in weak patients when the herb is administered on an empty stomach.¹² *Sutherlandia* is used traditionally during pregnancy with no adverse effect; however, scientific data do not exist to validate the use of the plant in pregnant women.¹² The dosage

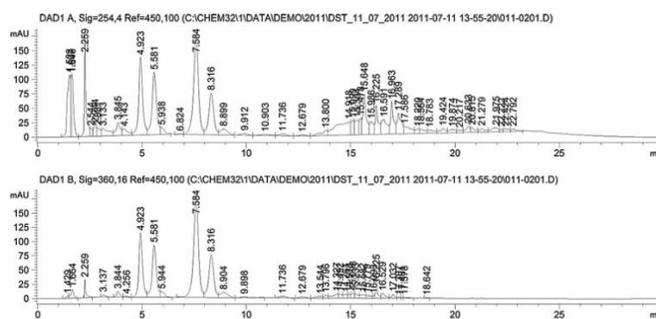
dispensed by traditional healers depends on the severity of the illness, age of the patient, and the nature of the complaint. Several reports of varying dosages exists in literature.¹

However, a scientific study recommended daily dose of *Sutherlandia* leaf powder is 9.0 mg/kg body weight, which is equivalent to two *Sutherlandia* tablets per day, each containing 300 mg of *Sutherlandia* dried leaf powder each. This dosage was drawn from the toxicology study on vervet monkeys (*Chlorocebus aethiops*), which further indicated that nine times the recommended dosage (81 mg/kg) administered daily for 3 months showed no significant changes to relevant hematologic, biochemical, and physiologic measures.⁴³ A recent phase I double-blind, placebo-controlled study (protocol TI-CIPSO01) conducted by the International Centre for Indigenous Phytotherapy Studies (TICIPS) through the South African Herbal Science and Medicine Institute (SAHSMI) at the University of the Western Cape on healthy individuals reported that 400 mg of leaf powder capsule twice a day for 3 months was tolerated without adverse effects.⁴⁴ The South African Ministry of Health encouraged the use of *S. frutescens* for the treatment of patients with AIDS.¹² Many patients therefore take traditional herbal medicines in conjunction with their modern antiretroviral medication, without recourse to the potential of drug–herb interactions.

Several studies on the interaction between antiretroviral drugs, such as nevirapine and atazanavir, and *Sutherlandia* extracts and its bioactives have been reported.^{45–47} In one of these studies, although l-canavanine increased the bioavailability and ultimately interaction with nevirapine in Caco-2 cells, no such effect was observed with the aqueous extract of *Sutherlandia*.⁴⁵ Long-term administration of *S. frutescens* extracts to male Sprague-Dawley rats for 5 days significantly reduced pharmacokinetic parameters (area under the curve and maximum concentration) of nevirapine.⁴⁶ Minocha and colleagues concluded from their preclinical results that co-administration of *Sutherlandia* along with low-therapeutic- index prescription drugs could lead to herb–drug interactions as well as limited efficacy of such drugs.⁴⁶

The aqueous and methanolic extracts of *S. frutescens*, as well as the terpenoid and flavonol glycoside fractions, varied in their influence on the accumulation of atazanavir by Caco-2 cells and also its metabolism in human liver microsomes.

FIG. 6. A high-performance liquid chromatography chemical profile of flavonoid constituents of dried *Sutherlandia frutescens* leaf powder extracted with methanol.



Although the aqueous extract reduced the absorption of atazanavir in the Caco-2 cells and the metabolism in human liver microsomes, the opposite was observed for the terpenoid fraction.⁴⁷ These herb–drug interactions may have important implications for the safety and efficacy of anti-retrovirals in immunocompromised patients.

***Sutherlandia* HIV/AIDS Clinical Trials: the Meeting of Science and Traditional Knowledge**

The popularity of herbal medicines has led to increasing concerns over their safety, quality, and efficacy. To this end, clinical trials have been conducted worldwide to ascertain the safety and efficacy of these herbal products using human participants. With regard to *S. frutescens*, several caregivers, such as Anne Hutchings, have treated HIV patients with *Sutherlandia* and other herbs weekly at Ngwelezana Hospital's AIDS clinic in northern KwaZulu-Natal. She observed that when taken with a proper diet, *Sutherlandia* improves quality of life and might be significant in delaying the need for antiretroviral therapy.⁴⁸

Reports such as this have prompted the funding of two separate trials by the governments of the United States and South Africa to clinically validate the claims of safety and efficacy. The National Institute of Health, through TICIPS, funded phase I and II clinical trials on the safety and efficacy of *Sutherlandia* leaf powder capsules in healthy and HIV-infected patients. Results of the phase I study have provided evidence of the safety of *Sutherlandia* in healthy people.⁴⁴ The South African government, through the Department of Science and Technology, is sponsoring a phase II trial to be conducted by SAHSMI using formulated *S. frutescens* capsules. This proposed trial aims to determine the safety and the effect of the formulated capsules on the markers of HIV progression in HIV patients. The study also aims to improve understanding of the pharmacokinetics of the formulated *Sutherlandia* capsules in the patients.

Intellectual Property Right Issues Regarding *Sutherlandia*

Acknowledging the value of indigenous knowledge in South Africa has brought to the fore the issue of protecting it and ensuring that knowledge holders are compensated for their contribution to the development of commercially traded products. To this end, South Africa is making a lot of effort to protect and encourage indigenous communities to use their natural resources and for its citizens to value traditional knowledge and innovation. However, identifying the ownership of the traditional knowledge of *Sutherlandia* as an antiviral agent has proved to be difficult. *Sutherlandia* has a history of medicinal use across several communities in South Africa. However, SAHSMI, through the Technology Transfer Office of the University of the Western Cape, is participating in discussions on bio-prospecting and intellectual property rights concerning use of *Sutherlandia* capsules in clinical trials for HIV/AIDS. Issues raised in this discussion include benefit sharing, bio-prospecting, and intellectual property rights.

Conclusion

S. frutescens is increasingly understood and studied as a phytomedicine that can potentially be used for people who are HIV positive but who do not yet qualify for antiretroviral treatment (*i.e.*, to fill the treatment gap). This can happen only if the clinical trials show that *Sutherlandia* is safe, is of good quality, and demonstrates efficacy. At the same time, greater collaboration between traditional health practitioners and scientists enhances insights into the use, preparation, therapeutic possibilities, and pharmaceutical make-up of this plant medicine. In this way, traditional knowledge and science intersect in new and original ways.

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Disclosure Statement

No competing financial interests exist.

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