



Review

A review of the taxonomy, ethnobotany, chemistry and pharmacology of *Sutherlandia frutescens* (Fabaceae)

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ABSTRACT

Sutherlandia frutescens (tribe Galegeae, Fabaceae), a popular plant in traditional medicine, is indigenous to South Africa, Lesotho, southern Namibia and southeastern Botswana. It is chemically, genetically and geographically extremely variable and has been divided into three subspecies and several regional forms. A second species, *Sutherlandia tomentosa*, is localized along the Cape coast. *Sutherlandia* is sometimes treated as part of the genus *Lessertia*. There are numerous vernacular names and a wide diversity of uses, including poor appetite, indigestion, stomach complaints, dysentery, colds, influenza, kidney conditions, fever, diabetes, internal cancers, uterine troubles, liver conditions, backache, rheumatoid arthritis, urinary tract infections, stress and anxiety, dropsy and heart failure. Notable is the use as a bitter tonic (“blood purifier”), anti-stress medication (*‘musa-pelo*) and, at least since 1895, specifically as a cancer tonic (both as treatment and as prophylaxis). Externally it is applied to haemorrhoids, inflamed wounds and eye infections. Recent *in vitro* and *in vivo* studies have shown antiproliferative, anti-HIV, anti-diabetic, anti-inflammatory, analgesic, antibacterial, anti-stress, anticonvulsant and antithrombotic activities. Aqueous extracts often differ in activity from organic solvent extracts. The presence of high levels of free amino acids, non-protein amino acids such as canavanine and GABA, the cyclitol pinitol, flavonols and triterpenes (including SU1, a cycloartane-type triterpene saponin) provide plausible hypotheses on how these compounds, individually or collectively, may be responsible for the reputed efficacy in a wide range of ailments. Results of animal studies, as well as a phase I clinical study, have shown no indications of toxicity. Sufficient preclinical data are now available to justify controlled clinical studies.

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1. Introduction

Sutherlandia frutescens (L.) R.Br. (widely known as cancer bush) has a long history of medicinal use in southern Africa. It has been used in the traditional medicine systems of different cultural groups (including the Zulu, Xhosa, Sotho, Khoi-San and Cape Dutch) for a wide diversity of ailments, amongst others, the treatment of stomach ailments, diabetes, internal cancers, stress, fever and wounds.

Small-scale cultivation and commercialization started in 1990, when air-dried leaves were supplied to a health shop in Port Elizabeth in the Eastern Cape Province. More recently (2000), a company called Phyto Nova (Pty) Ltd. initiated large-scale cultivation (Fig. 1A) and contract manufacturing of tablets made from powdered herb (i.e. thin stems and leaves – Fig. 1E). *Sutherlandia* tablets became popular as an adaptogenic tonic, claimed to be of value in stimulating appetite and reported to counteract the muscle-wasting effects of HIV-AIDS. In recent years, there has been a marked increase in both scientific and commercial interests in *Sutherlandia*. The aim of this paper is to summarize and review published and some unpublished scientific information about this important southern African medicinal plant.

2. Taxonomy

2.1. Description and relationships

Sutherlandia frutescens represents a variable species complex endemic to southern Africa (including the southern parts of Namibia, the extreme southeastern corner of Botswana, the western, central and eastern parts of South Africa and most of Lesotho). A second species, *Sutherlandia tomentosa* Eckl. & Zeyh., has a restricted distribution on coastal dunes along the coast near Cape Town. Both species are used in traditional medicine but there are distinct local preferences for particular forms of *Sutherlandia frutescens*. The genus *Sutherlandia* belongs to the tribe Galegeae and is closely related to the genera *Astragalus* L. and especially *Lessertia* DC. (sometimes subsumed under it, see later).

Sutherlandia frutescens (Fig. 1) is a prostrate to erect, perennial but short-lived shrub varying in height from less than 0.2–2.5 m. Stems are glabrous or sparsely pubescent, with numerous leaves borne mainly towards the tips. The leaves are shortly petiolate, stipulate and pinnate, with ± 8 pairs of opposite leaflets plus a terminal leaflet. Each leaflet is ovate-oblong, elliptic to narrowly oblong and varies from glabrous to sericeous, depending on the provenance. Spectacular red (very rarely white) flowers are borne in few-flowered axillary racemes. Each flower is tubular, markedly compressed laterally, with oblong, boat-shaped keel petals, two minute wing petals and a large, apically recurved standard petal, typically marked with white lines. The characteristic fruits are large, bladderly and papery pods, which may be broadly ovate to oblong, depending on the provenance. Each pod bears numerous pale brown to dark brown, laterally compressed, kidney-shaped, smooth to markedly rugose seeds.

Traditionally, a narrow species concept was followed (Phillips and Dyer, 1934) and six species were recognized: (1) *Sutherlandia frutescens* (L.) R.Br. (erect to procumbent, with ovate pods, up to

twice as long as wide); (2) *S. humilis* E. Phillips & R.A. Dyer (prostrate, very small, ± 0.2 m, with broadly ovate pods); (3) *S. microphylla* Burch. ex DC. (erect, up to 2.5 m, with linear, relatively narrow pods, more than twice as long as wide); (4) *S. montana* E. Phillips & R.A. Dyer (erect, up to 2 m, with ovate and somewhat sericeous leaflets and ovate pods); (5) *S. speciosa* E. Phillips & R.A. Dyer (procumbent to erect, up to 1 m, with ovate but resupinate pods; at maturity, the pod becomes pendulous, so that the upper, seed-bearing suture is directed downwards); (6) *Sutherlandia tomentosa* Eckl. & Zeyh. (erect to procumbent, 0.5–1.5 m high, with densely tomentose leaflets).

Field studies over a period of many years have shown that only two species should be recognized, with several, more or less geographically separated subspecies. Using enzyme electrophoresis, Moshe et al. (1998) has shown that the six species listed above are hardly distinct as the specific level and that only two species should be recognized, namely *Sutherlandia tomentosa* and *Sutherlandia frutescens* sensu lato, the latter to include all of the remaining “species” listed above. Moshe (1998) proposed the following treatment of the species:

1. *Sutherlandia tomentosa* Eckl. & Zeyh. – adaxial leaflet surface densely tomentose (the upper lamina completely obscured by hairs); leaflets rounded to obovate, often with the apex deeply emarginate. This species has a relatively localized distribution in the Western Cape Province, where it is found only on coastal dunes, between Koeberg and Still Bay.
2. *Sutherlandia frutescens* (L.) R.Br. – adaxial leaflet surface glabrous to sparsely sericeous (upper leaf lamina visible between the hairs); leaflets ovate-oblong to narrowly oblong and the apex obtuse, rounded or only slightly emarginate. This species, in its broad circumscription, is widely distributed, with three as yet unpublished subspecies and several regional forms.
 - 2a. “subsp. *frutescens*”. Fruit stipe directed towards the seed-bearing suture. This is a variable and geographically widespread subspecies that can be subdivided into four more or less recognizable forms.
 - Form 1. (typical form) – procumbent, glabrescent, up to 0.3 m high, with small flowers and ovate, much inflated pods. This form (Figs. 1C and D) has a wide distribution in the western and central parts of South Africa, the central and southern parts of Namibia and southern Botswana.
 - Form 2. (hairy form) – similar to the typical form but the twigs and leaves are densely pubescent. This form is restricted to coastal dunes in South Africa, from Port Nolloth to Wilderness near George (the distribution partly overlaps with that of *Sutherlandia tomentosa*). Genetic evidence (Moshe et al., 1998) indicated that this form is a product of introgression between the typical form of *Sutherlandia frutescens* and *Sutherlandia tomentosa*, with which it is partly sympatric.
 - Form 3. (dwarf form, “*S. humilis*” form) – similar to the typical form but the habit is dwarf and prostrate (up to 0.2 m high) and the pods tend to be more globose. This form is widely distributed in the dry central parts of South

Africa (the Little Karoo, Great Karoo and northwards to the southern Free State Province).

Form 4. (high altitude form, “*S. montana*” form) – similar to the typical form but the habit is usually erect and the shrubs are often taller (up to 2 m), with larger flowers. The pod shape varies from ovate to somewhat oblong, but the stipe is directed upwards (i.e. in the direction of the seed-bearing suture).

- 2b. “subsp. *speciosa*”. Fruit stipe directed towards the lower suture. The flowers are usually very large and the stipe is longer than in the other subspecies. The fruit becomes resupinate and is then superficially identical to the fruits of subsp. *frutescens* (but note the position of the seed-bearing suture). This subspecies is endemic to Namaqualand (extreme western parts of the Northern Cape Province of South Africa and northwards into southern Namibia).
- 3c. “subsp. *microphylla*”. Fruit stipe in line with the pod. The habit is erect (height up to 2.5 m) and the fruits are typically narrow and oblong (more than twice as wide as long).

This subspecies (Fig. 1A and B) is widely distributed in the dry interior of South Africa, as far north as Gauteng and the Northwest Province.

Recently, Goldblatt and Manning (2000) proposed an alternative classification system by transferring *Sutherlandia* to the genus *Lessertia* DC., presumably on the assumption that *Sutherlandia* merely represents an adaptation to bird pollination. The two genera are similar and probably also closely related, but it remains to be demonstrated (by morphological or genetic analysis) that *Sutherlandia* is indeed nested within *Lessertia*. If the two taxa prove to be sister groups in a cladistic sense, then the traditional generic concepts should be retained. The transfer of *Sutherlandia* to *Lessertia* by Goldblatt and Manning (2000) necessitated a new name for *Sutherlandia tomentosa*. The correct names for the two species in *Lessertia* are therefore *L. frutescens* (L.) Goldblatt & J.C. Manning and *L. canescens* Goldblatt & J.C. Manning. In the interest of nomenclatural stability, it is recommended that the conservative option be followed (see Germishuizen and Meyer, 2003; Klopper et al., 2006).



Fig. 1. *Sutherlandia frutescens*. (A) Commercial plantation; (B) fruiting plant of commercial type (“subsp. *microphylla*”); (C) flowers of “subsp. *frutescens*”; (D) flowers and pods of “subsp. *frutescens*”; (E) dried product (sutherlandia herb).

2.2. Nomenclature

Scientific name: *Sutherlandia frutescens* (L.) R.Br. [syn. *Lessertia frutescens* (L.) Goldblatt & J.C. Manning].

Vernacular names: cancer bush, sutherlandia, balloon pea, turkey flower (English); *kankerbos*, *gansies*, *grootgansies*, *wildekeur(tjie)*, *keurtjie*, *rooikeurtjie*, *kalkoen(tjie)bos*, *kalkoenblom*, *belbos*, *kalkoenbelletjie*, *klapperbos*, *jantjie-bêrend*, *bitterbos*, *wildekeurtjie*, *eendjies*, *hoenderbelletjie* (Afrikaans); *Blasenstrauch*, *Krebsbusch*, *Sutherlandia* (German); *'musa-pelo*, *'musa-pelo-oa-nōka*, *motlepelo*, (Sesotho); *phetola* (Setswana); *insiswa*, *unwele* (isiZulu, isiXhosa). Of all the common names of Karoo plants listed by Powrie (2004), *Sutherlandia* had the highest number, with 25 names or variations. See also Smith (1966) for additional vernacular names in Afrikaans.

3. Ethnobotany

A precise summary of published and unpublished information on the traditional uses of *Sutherlandia* is given in Table 1. The wide diversity of uses is noteworthy, as are the explicit mention, in 1895, of tonic and anti-cancer uses (Smith, 1895). The traditional uses also suggest anti-diabetic, anti-stress, anti-tuberculosis, pain-relieving and wound-healing activities.

4. Chemistry

4.1. Free amino acids

In common with many members of the family Fabaceae, the leaves of *Sutherlandia* contain high levels of free and protein-bound amino acids (Moshe, 1998; Van Wyk et al., unpublished data), making it a valuable and palatable fodder plant (Van Breda and Barnard, 1986; Le Roux et al., 1994; Shearing and Van Heerden, 1994). Analyses of leaves of commercial *Sutherlandia* (the so-called Phyto Nova SU-1 type) grown at different localities showed high levels of the free amino acids asparagine (1.6–35.0 mg/g), proline (0.7–7.5 mg/g) and arginine (0.5–6.7 mg/g) (Van Wyk et al., unpublished data). The presence of L-arginine is important, as this compound is an antagonist of L-canavanine that attenuates its anti-proliferative activity (see later).

4.2. Non-protein amino acids

Non-protein amino acids are commonly found in the seeds of Fabaceae (Bell, 1958; Bell et al., 1978). One of the most common compounds is L-canavanine (Fig. 2), a seed metabolite recorded from many members of the legume family (e.g. lucerne or alfalfa, *Medicago sativa* L.). The discovery of high levels of canavanine in *Sutherlandia* leaves by Moshe (1998) was therefore of considerable interest (Van Wyk et al., 1997). Not only did it give some explanation for the traditional use of *Sutherlandia* against cancer, but it also appears to be the first known case of a canavanine-containing plant having a well-recorded history of use against cancer (see Table 1). The level of canavanine in leaves from different species and populations of *Sutherlandia* was found to be very variable, from 0.42 mg/g to 14.5 mg/g (Moshe, 1998) and about 1.3–3.1 mg/g in commercial *Sutherlandia* (SU-1 type) (Van Wyk et al., unpublished data). Analyses of the same type of *Sutherlandia* by Tai et al. (2004) confirmed the presence of canavanine in commercial material and recorded a level of 3 mg/g dry weight.

Canavanine has documented anticancer (Crooks and Rosenthal, 1994; Swaffar, 1995; Rosenthal, 1997; Bence et al., 2002) and anti-

ral activity, including inhibition of influenza virus and retroviruses (Green, 1988).

The presence of γ -aminobutyric acid (GABA) (Fig. 2) may also be relevant, as commercial samples contain 0.23–0.85 mg/g (Van Wyk et al., unpublished data). GABA is an inhibitory neurotransmitter that could partly account for the use of *Sutherlandia* to treat anxiety and stress (see later). It has also been found to inhibit tumor cell migration (Ortega, 2003).

4.3. Pinitol

Early studies by Snyders (1965), Viljoen (1969) and Brümmerhoff (1969) showed the presence of the cyclitol called ino-inicytol (also commonly known as pinitol – Fig. 2) in *Sutherlandia microphylla* leaves. Using pure pinitol as a reference standard in HPLC analyses with a refractive index detector, Moshe (1998) reported a level of up to 14 mg/g dry weight in the leaves. The recorded bioactivities of pinitol make it a potentially important compound in the context of the traditional uses of *Sutherlandia* against diabetes and inflammation (see later). Pinitol is a known anti-diabetic agent that may have an application in treating wasting in cancer and AIDS (Ostlund and Sherman, 1996). It exerts an insulin-like effect, resulting in lower blood sugar levels and increased availability of glucose for cell metabolism (Bates et al., 2000) and augments the retention of creatinine by muscle cells (Greenwood et al., 2001). Pinitol therefore seems to play a role in regulating cellular energy, resulting in increased energy levels and a reduction in fatigue.

4.4. Flavonoids

Sutherlandia leaves are known to contain at least six flavonoids (Moshe, 1998). Preliminary structural elucidation has indicated that these are flavonol glycosides (D. Olivier et al., unpublished data).

4.5. Triterpenoid saponins

Triterpene glycosides were first detected in *Sutherlandia microphylla* leaves by Brümmerhoff (1969) and Viljoen (1969) but the chemical structures were not determined. Gabrielse (1996) isolated a pure compound (later called SU1) from extracts of *Sutherlandia frutescens* (*S. microphylla*). Moshe (1998) reported a complex pattern of triterpenes in the various species and forms of *Sutherlandia*, with limited variation within populations but large differences between populations. The major triterpene in commercial *Sutherlandia* material is a cycloartane-type triterpene glycoside called SU1 (Fig. 2). Its structure has been determined by Olivier et al. (submitted for publication in *Journal of Natural Products*) as (24R)-25- β -D-glucopyranosyloxy-3 α ,7 α ,24-trihydroxycycloartane. At least 56 different triterpene glycosides have been detected in various provenances of *Sutherlandia* and structural elucidation of the main compounds is ongoing (D. Olivier et al., unpublished data). The mixture of cycloartane-type triterpenoid glycosides also varies geographically in South Africa (C. Albrecht, unpublished results).

4.6. Other compounds

Thai et al. (2004) reported the presence of hexadecanoic acid, γ -sitosterol, stigmast-4-en-3-one and at least three long chain fatty acids. Studies in our laboratory have shown that *Sutherlandia* leaves contain very high levels of as yet unidentified polysaccharides,

Table 1
Chronological list of ethnobotanical anecdotes for *Sutherlandia*, including some from unpublished sources

Source or reference	Anecdotes and uses (cited verbatim from the referenced texts, or directly translated from the Afrikaans)
Pappe (1847) Smith (1895)	Page 6: dried and pulverised roots and leaves used for eye diseases Page 62: preparation of leaves as tonic; page 66: pinch of leaves in boiling water taken twice or thrice a day for extreme weakness and sinking at the stomach; page 86: blood purifier; page 116 & 117: leaf decoction for dysenteric diarrhoea; page 188 & 189: curing of malignant tumours, cancerous in appearance; also used as blood purifier and tonic . . . to delay the progress of true cancer and much prolonged life
Dykman (1908)	Page 145: infusion of bark and leaves for cancer, stomach ailments and blood purification – one cup three times a day until it starts working, then a little less
Kling (1923) Laidler (1928)	Page 20: leaf juice mixed with fat or (leaf-) lard as blisterplaster – “treksalf” – for infections, pustules and carbuncles Page 443: decoctions for washing wounds; given to drink for fevers; also used for consumption, chicken pox, etc. – the “etc.” implies a wide range of ailments, i.e. a general medicine or tonic use
Anonymous (1962) Watt and Breyer-Brandwijk (1962)	Page 146: knife tip of powdered dried leaves after each meal for liver ailment – “lewerkwaal” Page 649: Infusions or decoctions of the leaf and bark are used for influenza, stomach complaints, intestinal complaints, internal cancers, uterine troubles, liver diseases, rheumatism, inflammations, haemorrhoids, dropsy, backache and as a tonic; infusions are taken in amenorrhoea, as blood tonic and as cancer prophylactic; powdered leaf in syrup is used to treat cough; weak infusions taken before meals seem to act as a bitter tonic to improve appetite and digestion; may cause sweating, may be slightly purgative and may be emetic if too strong
Smith (1966)	Pages 275 and 276: decoctions used for washing wounds and taken internally for fevers, chicken-pox and especially for cancer
Anonymous, undated. <i>Kruieresepte van die Montagu Museum</i> (“Herbal recipes from the Montagu Museum”). Based on indigenous knowledge collected by Mr Kobus Kriel (unpublished notes)	Page 2: cancer, wounds, fever, blood purification – dried, pounded plant taken as a tincture
Archer (1990)	Page 966: infusion of leaves and flowers used for stomach complaints; page 967: basic ingredient in most medicines in Namaqualand – mostly for stomach ailments, in Table 3, also listed specifically for influenza, wounds, pains, aches and skin disorders
Cillié, A.M., 1992. <i>Kruie op witblits, rate, resepte en feite</i> , pp. 43. Unpublished notes, Worcester Museum	Page 17: leaves steeped in brandy used for back ailments and kidney ailments; leaf infusion (“tea”) made from the whole plant used to treat cancer and also to wash wounds
Palmer (1985)	Page 124: half cup of infusion or decoction three times a day for cancer, fever and as blood purifier; decoction of root and leaves as eye wash
Rood (1994)	Pages 53 and 54: decoction of leaves for cancer growths; leaf infusions used for influenza, stomach complaints, cancer, chicken-pox, and the common cold; dried powdered leaves snuffed for head cancer and nose cancer; leaf infusion used for diabetes and as eye wash for weak eyes; flowers in strong decoction for fever and to wash wounds; decoction also drunk (taken internally) for “stomach nerves” and varicose veins; infusion of bark and leaves used as tea, mainly to cure haemorrhoids)
Shearing and Van Heerden (1994) Van Breda and Barnard (1986) Van Wyk et al. (1997)	Page 82: washing wounds, fevers, chicken-pox and cancer Page 1 and 2: dried leaf and flower used as snuff for head cancer and infusion of leaf used for stomach cancer Page 246: stomach problems, cancer; bitter tonic, good general medicine; colds, influenza, chicken-pox, diabetes, varicose veins, piles, inflammation, liver problems, backache, rheumatism; washing of wounds, fever
Maliehe (1997) Van Wyk and Gericke (2000)	Fits, circulation problems, stress-related ailments and chronic illness Page 148: tonic to treat fever, poor appetite, indigestion, gastritis, oesophagitis, peptic ulcer, dysentery, cancer prevention, cancer treatment, diabetes, colds, influenza, cough, asthma, chronic bronchitis, kidney conditions, liver conditions, rheumatism, heart failure, urinary tract infections, stress and anxiety; pancreatic cancer, other cancer, improved quality of life in patients with terminal metastatic breast cancer; rheumatoid arthritis
Von Koenen (2001)	Page 182: leaf tea used for internal cancer . . . also for chicken-pox to reduce fever (also as additive to bath water) and as eye drops. In a diluted form, for influenza, rheumatism, liver problems, haemorrhoids (externally in concentrated form), for disease of the bladder and uterus, stomach conditions and backache. Taken as a tonic before meals, <i>Sutherlandia</i> stimulates appetite and digestion
Thring and Weitz (2006)	An infusion of 3 teaspoons/small handful of leaves and stems in 1 l water taken in the morning and evening for back pain, bladder and kidneys, cancer, colds, influenza, liver, diabetes, fever and stomach complaints
Van Wyk et al. (2008). The local experts were: AS = Andries Salmon, EW = Ernest Williams, JO = Jan Oormeyer, KS = Kiewiet (“Hottie”) Steenkamp, PC = Piet Cupido, PT = Poppie Teo and WdT = Willem du Toit	AS: high blood pressure – drink powdered leaf as tea (can be drunk often; <i>Sutherlandia frutescens</i> is better than <i>S. microphylla</i>), EW: stomach problems – drink as tea; the short one (<i>Sutherlandia frutescens</i>) is female and is used for men’s problems and the long one (<i>S. microphylla</i>) is male and is used for women’s problems. JO: back pain and kidney pain (as general cleanser or blood purifier) – steep the leaves of three twigs in a small pot and drink after a meal (not on an empty stomach); “short one” (i.e. <i>Sutherlandia frutescens</i>) works better. KS: back pain or stomach pain (“short one is better”). PC: general medicine – drink with honey (“the short one is better”). PT: cancer (for improvement, not as a cure – but no own experience) – infusion of fresh or dried leaves (two twigs per cup, not poisonous). WdT: cancer and “all ailments”
Vergoes Houwens, N.F. no date. <i>Medicine from the Veld</i> . Unpublished notes, Worcester Museum	Page 2: weak leaf infusion taken for internal cancers; also for fever, as blood purifier and to wash wounds; root and leaf infusion for eye bath
Wileman, L. no date. <i>The uses of our Karoo plants in bygone times</i> . Unpublished notes, Worcester Museum	Page 7: washing wounds, fevers, chicken-pox, cancer, eye wash
Youthed, G. (Ed.) no date. <i>Dictionary of South African traditional medicinal plants of the Eastern Cape</i> . Pharmaceutical Society of South Africa, Johannesburg (unpublished)	Page 158: leaves, stems and roots used for blood purification, as tonic, for chest colds – powdered leaf mixed with sugar – and abdominal complaints; said to delay the course of cancer
B.-E. van Wyk (unpublished data)	70 g of leaves, stems and pods boiled in 2 l of water until reduced to 1.5 l [this is a 2-week supply, i.e. the daily dose is ca. 5 g in decoction – the recipe came from local Khoi-San sheepshearers]. “Four good swigs” taken in morning and midday (not in the evening) for high blood pressure, obesity and improved energy. [No side effects noted after 6 years of continual use, except insomnia when taken in the evening]

Table 1 (Continued)

Source or reference	Anecdotes and uses (cited verbatim from the referenced texts, or directly translated from the Afrikaans)
C. Albrecht (unpublished data)	A 65-year old male was clinically diagnosed with cancer of the head of the pancreas due to jaundice, CT-scanning, enlarged gall bladder, epigastric mass, endoscopic retrograde cholangiopancreatography (ERCP) and laparotomy by an experienced surgeon at a teaching hospital. He received a by-pass to relieve the jaundice and was discharged. He decided to self-medicate and chose to use the pods of <i>Sutherlandia frutescens</i> because he remembered that this was from the kankerbos (cancer bush). This happened in December 1992 when <i>Sutherlandia</i> plants had lost most of their leaves but had numerous pods. He made a water decoction and drank the extract of 1 g dry weight a day for 45 days after which he felt so good that he returned to work. Four years later he was re-examined at a teaching hospital by the same surgeon with CT-scans and no detectable sign of the epigastric mass could be found. He lived 5 years post diagnosis and died of kidney failure which was unrelated to his pancreas pathology

resulting in aqueous extract yields of up to 35% of dry weight (D. Olivier et al., unpublished data).

5. Pharmacological properties

5.1. Cancer

Sutherlandia has become widely known as cancer bush because of the reported use by Khoi-San and Cape Dutch people against internal cancers (Table 1). There are unpublished anecdotes of cancer patients who experienced an improved quality of life and survived for much longer than expected (and some that were apparently cured) after treatment with *Sutherlandia* (Van Wyk and Gericke, 2000; C. Albrecht, unpublished data – Table 1). Clinical evidence for the reduction of fatigue in 16 cancer patients was presented by Grandi et al. (2005).

The discovery of canavanine as a major leaf metabolite in *Sutherlandia* therefore seems to be more than just a coincidence although concentrations required for cancer cell kill in vivo would also be toxic and no toxicity was found (Seier et al., 2002). Furthermore, it is now also known that the major triterpenoids of *Sutherlandia* are structurally closely related to cycloartane-type triterpenoids with proven cancer chemopreventive activity (Kikuchi et al., 2007).

Using ethanolic extracts, Tai et al. (2004) provided the first in vitro evidence of anti-cancer effects by showing a concentration dependent 50% inhibition of proliferation of MCF7, MDA-MB-468, Jurkat and HL60 cells. It was suggested that canavanine may play a role in the antiproliferative effects but that some other factors must also be involved because addition of arginine (antidote for canavanine) did not abrogate the antiproliferative effect. Na et al. (2004) reported that methanol extracts of *Sutherlandia* inhibited the DNA binding of NF- κ B activated by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in MCF10A human breast epithelial cells in a dose-dependent manner. They concluded that the inhibition of TPA-induced COX-2 expression through suppression of DNA binding of NF- κ B may contribute to chemopreventive or chemoprotective activity in *Sutherlandia*. Chinkwo (2005) demonstrated that aqueous whole plant extracts induced apoptosis in neoplastic cells, notably cervical carcinoma and CHO (Chinese Hamster Ovary cells) cell lines. In contrast, Steenkamp and Gouws (2006)

did not observe significant cytotoxic effects when aqueous extracts of *Sutherlandia* was tested against three human cancer cell lines (DU-145 prostate cancer cells, malignant MDA-MB-468, and MCF7 breast cancer cells and non-malignant MCF-12A breast cells). Using the Ames test, dichloromethane extracts of *Sutherlandia* were found to exhibit antimutagenic activity (Reid et al., 2006) and it was concluded that it has potential to act as anticarcinogen or chemopreventative agent. Chen (2007) tested polar and non-polar extract of *Sutherlandia*, all of which were found to have growth inhibition effects against PC-3 and LNCaP human prostate tumor cell lines in a dose dependent manner. It was concluded that canavanine is partly responsible for the anti-carcinogenic activity but that the effects is likely to be due to other compounds as well. A detailed study by Stander et al. (2007) on the effects of a 70% ethanol extract on MCF-7 human breast adenocarcinoma cells showed statistically significant time-dependent and dose-dependent effects on cell numbers, morphology and gene expression profiles. Valuable information on molecular mechanisms and signal transduction was obtained by microarray analysis.

The possibility that canavanine is not the only active compound is supported by Kikuchi et al. (2007), who studied the cancer chemopreventive activity of 48 natural and semisynthetic cycloartane-type triterpenoids. Many of the compounds (so-called astragalosides) are known from the genus *Astragalus* L., also a member of the tribe Galegeae and related to *Sutherlandia*. It is interesting to note that the most powerful inhibitory effects in an in vivo mouse skin carcinogenesis test was found in cycloartanes with hydroxylation at C-24 and with a 3-oxo group. This configuration is present in SU1 (Fig. 2), the main cycloartane of the commercial type of *Sutherlandia*.

5.2. HIV and AIDS

Claims have been made that *Sutherlandia* tablets used as a tonic by AIDS patients resulted in an improvement of mood and appetite, weight gain, improved CD4 counts and reduced viral loads (Gericke et al., 2001; Morris, 2001; Chaffy and Stokes, 2002; Van Wyk, 2004). These claims have resulted in a NIH NCAM-sponsored clinical study to evaluate the possible effects of *Sutherlandia* on cachexia (the muscle-wasting effects seen in patients with cancer, tuber-

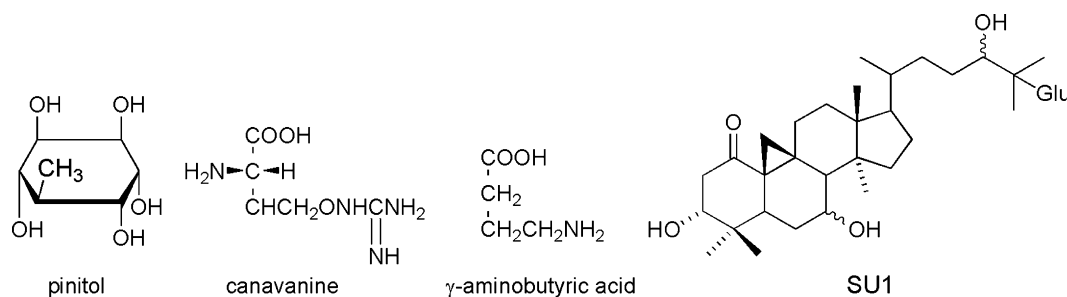


Fig. 2. Chemical structures of the compounds from *Sutherlandia frutescens*.

culosis and AIDS). A phase I study has shown that *Sutherlandia* is well tolerated and that it showed no significant side effects (Johnson et al., 2007). A phase II study is said to be currently underway. It has been speculated that *Sutherlandia* triterpenoids might have corticomimetic activity besides the anticipated bitter tonic (*amara*) effects (Van Wyk and Wink, 2004). The claimed immunostimulant activity of the related, and chemically similar *Astragalus membranaceus* (Fisch.) Bunge, is noteworthy (World Health Organization, 1999), but there is as yet no convincing evidence from human studies. In vitro experiments of the effects of organic and aqueous extracts of *Sutherlandia* on HIV target enzymes (including HIV reverse transcriptase) by Harnett et al. (2005) and Bessong et al. (2006) showed that there are some compounds in aqueous extracts responsible for inhibitory effects. The mode of action is not yet known. Canavanine is an inhibitor of nitric oxide synthase and has potential for the treatment of septic shock (Anfossi et al., 1999; Levy et al., 1999), a condition associated with advanced stages of AIDS. Tai et al. (2004) considered the lack of inhibition of NO secretion in their study to be concentration related. In a review of available evidence for the value of *Hypoxis* and *Sutherlandia* in treating HIV, Mills et al. (2005) noted the absence of clinical trials and warned against possible interactions with antiretroviral drugs.

5.3. Diabetes

Sutherlandia is widely used, especially along the western coastal region of South Africa, for the treatment of diabetes (Rood, 1994; Van Wyk et al., 1997; Van Wyk and Gericke, 2000). In some places (e.g. at Nieuwoudtville; Willem Steenkamp, pers. comm. to BEvW), this is the only recorded traditional use, despite a rich local folklore of other medicinal plants and their uses. The high level of pinitol in *Sutherlandia* leaves was proposed by Moshe (1998) and Van Wyk et al. (2000) as a plausible rationale behind the traditional anti-diabetic use. A review of the limited available pharmacological evidence was presented by Sia (2004). It was argued that L-canavanine, other amino acids such as L-arginine and pinitol may contribute to anti-diabetic effects, either directly or via anti-inflammatory and NO-inhibitory activity. The anti-inflammatory and NO-inhibitory activity of *Sutherlandia* extracts could counteract the insulinitis of autoimmune diabetes by protecting pancreatic beta-cells against reactive oxygen radicals of which NO is one.

Bates et al. (2000) have shown that pinitol exerts an insulin-like effect by reducing blood sugar levels in diabetic mice. A preliminary study of the clinical benefits of pinitol in obese and mild type 2 diabetic individuals showed disappointing results (Davies et al., 2000). Ojewole (2004) presented evidence that *Sutherlandia* extracts can reduce glucose uptake in STZ-treated mice. Using Wistar rats fed on a diabetogenic diet, Chadwick et al. (2007) showed statistically significant increases in glucose uptake in peripheral tissues, a reduction in intestinal glucose uptake and no weight gain in pre-diabetic rats receiving *Sutherlandia* via their drinking water. The authors concluded that *Sutherlandia* extracts show promise as a medication for type 2 diabetes but that the clinical efficacy and mechanisms of action need further study.

5.4. Inflammation, pain and wounds

Amongst the diversity of traditional uses of *Sutherlandia* listed in Table 1, the treatment of inflammatory conditions and wounds is a recurrent theme since the earliest published records. Recent studies have indicated that *Sutherlandia* extracts have anti-inflammatory, analgesic and antibacterial activity.

In a study of anti-inflammatory effects of the topical application of *Sutherlandia* extracts on mouse skin stimulated with a

prototype tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), Kundu et al. (2005) demonstrated in vivo inhibition of the expression of cyclooxygenase-2 (COX-2). Possible mechanisms of the inhibition of COX-2 were discussed, as well as the link between anti-inflammatory and chemopreventative activity. An earlier in vitro study by Na et al. (2004) led to the same conclusions. Tai et al. (2004) did not see significant antioxidant effects but Ojewole (2004) recorded statistically significant anti-inflammatory effects in reducing fresh egg albumin-induced pedal oedema in mice. He also recorded in vivo analgesic activity. Fernandes et al. (2004) noted the link between antioxidant and anti-inflammatory activities and reported that hot water *Sutherlandia* extracts have superoxide and hydrogen peroxide scavenging activities at concentrations as low as 10 µg/ml. Using the DPPH free-radical scavenging assay, Katerere and Eloff (2005) showed that acetone extracts have antioxidant activity, while Chen (2007) found activity in both polar and non-polar extracts. The study of Katerere and Eloff (2005) was the first to report antibacterial activity (of hexane extracts) against *S. aureus*, *S. faecalis* and *E. coli* at MIC values of 0.31, 1.25 and 2.50 mg/ml, respectively. In the context of wound-healing, it should be noted that canavanine has patented anti-viral activity (Green, 1988). The earliest recorded uses of *Sutherlandia* (Table 1) refer to the treatment of eye ailments.

5.5. Stress

In Lesotho traditional medicine, *Sutherlandia frutescens* is one of several species of shrubby legumes, collectively known as '*musa-pelo*', that have been traditionally used to treat stress-related ailments, shock, trauma, fits and severe depression (Moteeteete and Van Wyk, 2007). In Lesotho, stress and grief are thought to affect the heart first, so that these medicines are aimed at treating the heart ('*musa-pelo* means "to turn the heart around" or "the one who brings back health to the heart"). The statement "for ages and ages, the Basotho people have used *Sutherlandia* for trauma and chronic illness", was recorded by one of us (BEvW) during an interview with Eric Maliehe (a Basotho traditional healer) on 22 September 2000. The Zulu name *insiswa* ("the one which dispels darkness") and the Tswana name *phetola* ("it changes") both allude to the reversal of stress-related conditions. The frequent mention of "tonic" and "blood purifier" (Table 1) may also relate to possible adaptogenic effects. The term *adaptogen* was first used by the Russian scientist Lazarev in 1947 as a substance that creates "non-specific increased resistance" (Brekhman and Dardymov, 1969). Adaptogens are defined as substances that cause minimal physiological changes, have a broad spectrum of activity and have a non-directional normalising effect (i.e. they can activate or inhibit, depending on the imbalance that needs correction).

Stress-related ailments are known to be linked to the endocrine system. Van Wyk and Wink (2004) have hinted at possible corticomimetic activity. The effects of *Sutherlandia frutescens* on steroidogenesis was investigated by Prevoo et al. (2004) and Smith and Myburgh (2004). Using a model of chronic intermittent immobilization stress in adult male Wistar rats, it was shown that treatment with *Sutherlandia* extract resulted in a statistically significant reduction in corticosterone levels. It was also found that chloroform extracts have a greater inhibitory effect than methanolic extracts on progesterone and pregnenolone metabolism. It has been suggested (Sia, 2004; Tai et al., 2004) that γ -aminobutyric acid (GABA) may play a role in the improvement of the mood of patients with chronic ailments. These results provide an alternative hypothesis on the mechanism of action of *Sutherlandia* as a traditional anti-stress therapy. More recently, Prevoo et al. (2008)

showed that *Sutherlandia* attenuates adrenal P450 enzymes, which may indicate a possible mechanism by which glucocorticoid levels (and symptoms of stress) are reduced.

5.6. Other indications

Ojewole (2008) studied an as yet unrecorded and unpublished traditional use for *Sutherlandia* (Table 1), namely the treatment of childhood seizures and epilepsy. In vivo studies indicated that *Sutherlandia* extracts (25–400 mg/kg, intraperitoneal) had statistically significant anticonvulsant activity in mice. Recently, Kee et al. (2008) reported that *Sutherlandia frutescens* aqueous leaf extracts displayed antithrombotic activity, with an IC50 value of 2.17 mg/ml. Finally, there has been several recent anecdotes that *Sutherlandia* is effective in alleviating the symptoms of heartburn.

5.7. Toxicology

The long history of traditional use, with no reports of any serious side effects, suggests that *Sutherlandia* can be considered as generally safe. The only side effects that have been recorded are dryness of the mouth, occasional mild diarrhoea or mild diuresis and dizziness in cachectic patients (Mills et al., 2005). In rural areas, infusions of “two or three leafy twigs” are considered to be a safe and effective daily dose. The various recipes recorded by one of us (BEVW) suggest that infusion or decoctions of 2.5–5 g of dry material per day can be regarded as the traditional dose. One cup of infusion per day (ca. 2.5 g) was considered to be an effective dose by Dykman (1908) (Table 1). The highest recorded dose is a decoction of 5 g of leaves, stems and pods taken daily in the morning and midday for a period of more than 6 years without any ill effects (B-E. van Wyk, unpublished data – see Table 1). Ojewole (2004) studied acute toxicity in fasted Balb C albino mice (20–25 g) by intraperitoneal administration of graded aqueous extracts of *Sutherlandia frutescens* var. *incana*. The calculated median lethal dose (LD₅₀) was 1280 ± 71 mg of extract per kg, which led to the conclusion that crude extracts of *Sutherlandia* are probably relatively safe in mammals (Ojewole, 2004). For commercial preparations, 300 mg of dried leaves twice per day (i.e. 600 mg per day) is recommended (with the usual precaution that it should be avoided during pregnancy or lactation). This rather conservative dose was taken as a basis for calculating the dosage levels of a detailed safety study in vervet monkeys (Seier et al., 2002). Monkeys were given 0, 1, 3 and 9 times the recommended daily dose of 9.0 mg/kg body weight (i.e. 0, 9.0, 27.0 and 81.0 mg of leaf powder) administered as part of a carefully monitored standard diet for a period of 3 months. No clinically significant toxic or side effects were observed in a detailed evaluation of 15 haematological, 21 clinical biochemical, six physiological and several behavioural variables (Seier et al., 2002).

A phase I clinical study of 25 healthy adults at the Karl Bremer Hospital, Bellville, South Africa (Johnson et al., 2007) has shown that two 400 mg leaf powder capsules (800 mg per day) was well tolerated, with no side effects noted during or after the 3 months trial period. There was no change in the frequency of adverse events, nor any clinically significant changes in most physical, vital, blood and biomarker indices. A statistically significant increase in appetite was noted in the treatment group, as well as a lower respiration rate ($P < 0.04$), a higher platelet count ($P < 0.03$), MCH ($P < 0.01$), MCHC ($P < 0.02$), total protein ($P < 0.03$) and albumin levels ($P < 0.03$). These differences remained within the normal physiological range, and were not considered clinically relevant.

It is possible that products containing *Sutherlandia* may interact with antiretroviral medication (Mills et al., 2005) or with insulin or other diabetes medication (Sia, 2004).

6. Conclusion

Sutherlandia frutescens represents a species complex showing a mosaic of morphological and chemical characters. Distinct geographical discontinuities have been recorded within the genus, suggesting two species (*Sutherlandia tomentosa* and *Sutherlandia frutescens*), with the latter comprising three subspecies and several regional forms. *Sutherlandia* is morphologically and chemically similar to *Lessertia*, *Astragalus* and other genera of the tribe Galegeae but there are as yet no convincing morphological and genetic evidence for subsuming the genus under *Lessertia*. Nevertheless, there are two alternative classifications systems, so that the plant can also be referred to as *Lessertia frutescens*.

Sutherlandia frutescens is an important traditional medicine in southern Africa that has been used by various cultural groups for a very wide range of indications. Early records are rare, but suggest that the Khoi-San and early Cape settlers used *Sutherlandia* as a general medicine and tonic against stomach ailments and internal cancers and as a topical application for treating wounds and eye infections. The preventative and possible curative uses of *Sutherlandia* against cancer was first explicitly recorded by Smith (1895). Other notable regional uses of *Sutherlandia* include diabetes, inflammatory conditions and stress-related ailments.

No detailed studies of the chemical diversity in *Sutherlandia* has yet been published but available information shows that the leaves contain complex mixtures of primary and secondary metabolites, notably amino acids, the non-protein amino acid L-canavanine, a cyclitol (pinitol) and several as yet unidentified flavonols. Also present are chemically complex and geographically variable mixtures of cycloartane-type triterpenoid glycosides, structurally similar to the astragalosides found in the genus *Astragalus*.

Recent in vitro and in vivo studies have shown a range of pharmacological activities that generally provide rather convincing support for the wide diversity of traditional uses that have been recorded. Recent studies have focused mainly on anti-cancer, anti-HIV, anti-diabetic, anti-inflammatory, anti-oxidant, analgesic and antibacterial activities. Some of the compounds present in *Sutherlandia* (notably L-canavanine, L-arginine, pinitol and cycloartane triterpenoids) are pharmacologically well known and provide additional supporting evidence for possible mechanisms of bioactivity. Many of the recent studies suggest that there are large differences in bioactivity between polar and non-polar extracts. Although clinical evidence is still lacking, there is a growing body of preclinical data that supports the potential use of *Sutherlandia* preparations for a range of ailments.

A detailed safety study in vervet monkeys has indicated no toxicity and no noteworthy side effects. An acute toxicity study in mice also suggested that *Sutherlandia* extracts have a low toxicity. The results of a clinical study (phase I) showed that 800 mg of leaf powder per day was well tolerated by healthy adults, with no side effects and no clinically significant differences between the treatment group and the placebo group.

The diversity of chemical compounds in *Sutherlandia* and the diversity of uses agree with the traditional concept of an adaptogen. It seems likely that some of the pharmacological activities are due to synergistic effects, as already indicated by Tai et al. (2004) and Chen (2007) in the case of antiproliferative activity. Considerable preclinical evidence has accumulated over the last 10 years, almost all of which indicates positive results for a range of test systems. It is suggested that the time has come for controlled clinical studies to properly evaluate the benefits and risks of using *Sutherlandia* as a treatment or adjuvant for chronic and serious health conditions.

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