Cancer Association of South Africa (CANSA)

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Fact Sheet
And Position Statement
on
Sutherlandia Frutescens

Introduction

Sutherlandia frutescens is a fairly widespread, drought-resistant medicinal plant indigenous to Southern Africa, and is commonly known as the "cancer bush." This plant has traditionally been used for the treatment of various ailments, although it is best known for its claims of activity against "internal" cancers.

"*Sutherlandia frutescens* [*S. frutescens*] is regarded as the most profound and multi-purpose of the medicinal plants in Southern Africa. Because of its efficacy as a safe tonic for diverse health conditions it has enjoyed a long history of use by all cultures in Southern Africa.

"Sutherlandia powerfully assists the body to mobilize its own resources to cope with diverse physical and mental stresses, and it should therefore be more correctly known as an adaptogenic tonic.

"The traditional Tswana name *Phetola* alludes to this: Phetola means *it changes*, meaning that the plant changes the course of many illness into a favorable outcome. (Similar to the European concept of an alterative). The North Sotho name *Lerumo-lamadi* means *the spear for the blood* meaning that Sutherlandia is a powerful blood-purifier or all-purpose tonic."
(Sutherlandia.org).

Botanical Description of *Sutherlandia frutescens*

Sutherlandia frutescens is a shrub of average (medium) size. Its leaves are green with a grey tinge to it. The plant has bright red butterfly-shaped flowers. Pollinated flowers produce balloon-like seedpods that has a slightly red tint.

The plant belongs to the class *Magnoliopsida*, order *Fabales*, genus *Sutherlandia*, and species *frutescens*. It comes from the Fynbos Biome of the Western Cape although it also grows in the Eastern Cape, Northern Cape, some areas of KwaZulu-Natal and Mpumalanga. The seeds are harvested from the wild, although it is grown in some community gardens and commercially on a few farms.

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This medicinal plant is known by various popular names:

- bitterbos (bitter bush - Afrikaans)
- blaasbossie (bladder bush for its balloon-like pods - Afrikaans)
- blaas-ertjie (balloon-like pea - Afrikaans)
- eendjie (duckling - Afrikaans)
- gansiekeurtjie (gosling - Afrikaans)
- hoenderbelletjie (the wattle of a cockerel - Afrikaans
- kalkoenbos (turkey bush - Afrikaans)
- kankerbos (cancer bush - Afrikaans)
- klappers (cracker from the noise it makes when stepped upon - Afrikaans)
- lerumo-lamadi (Sepedi)
- musa-pelo & motlepelo (Sesotho)
- phetola & mokakana (Setswana)
- umnwele (isiXhosa)
- unwele (isiZulu)

(Aboyade, *et al.,* 2014).

An Overview of Scientific Evaluation of Sutherlandia Frutescens

The *Sutherlandia frutescens* plant and its extracts have been extensively been researched. Herewith brief information from applicable research reports since 2011.

Antiretrovirals and HIV

The use of traditional/complementary/alternate medicines (TCAMs) in HIV/AIDS patients who reside in Southern Africa is quite common. Those who use TCAMs in addition to antiretroviral (ARV) treatment may be at risk of experiencing clinically significant pharmacokinetic (PK) interactions, particularly between the TCAMs and the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Mechanisms of PK interactions include alterations to the normal functioning of drug efflux transporters, such as P-gp and/or CYP isoenzymes, such a CYP3A4 that mediate the absorption and elimination of drugs in the small intestine and liver. Specific mechanisms include inhibition and activation of these proteins and induction via the pregnane X receptor (PXR). In their research, Müller and Kanfer (2011) show that several clinical studies and case reports involving ARV-herb PK interactions have been reported. St John's Wort, Garlic and Cat's Claw exhibited potentially significant interactions, each with a PI or NNRTI. The potential for these herbs to induce PK interactions with drugs was first identified in reports of in vitro studies. Other in vitro studies have shown that several African traditional medicinal (ATM) plants and extracts may also demonstrate PK interactions with ARVs, through effects on CYP3A4, P-gp and PXR. The most complex effects were exhibited by *Hypoxis hemerocallidea*, *Sutherlandia frutescens*, *Cyphostemma hildebrandtii*, *Acacia nilotica*, *Agauria salicifolia* and *Elaeodendron buchananii*. Despite a high incidence of HIV/AIDs in the African region, only one clinical study, between *efavirenz* and *Hypoxis hemerocallidea* had been conducted. However, Müller and Kanfer remain convinced that several issues/concerns still remain to be addressed and, therefore, more studies on ATMs are warranted in order for more meaningful data to be generated and the true potential for such interactions to be determined.

Müller, et al. (2012), in a study to determine the safety of consuming *S frutescens* made use of aqueous and methanolic extracts of *Sutherlandia frutescens* prepared by freeze-drying of hot water and methanol decoctions of *S. frutescens* plant material. The aim of their study was to determine the effects of extracts and phytochemical components of *Sutherlandia frutescens* on the *in vitro* absorption and metabolism of the

antiretroviral protease inhibitor, atazanavir. They found that the extracts and phytochemical components of *S. frutescens* influenced the accumulation of atazanavir by Caco-2 cells and also affected ATV metabolism in human liver microsomes. They are of the opinion that these interactions may have important implications on the absorption and metabolism and thus the overall oral bioavailability of atazanavir.

The objective of a follow-up study by Müller, et al. (2013) was to investigate the effect of Sutherlandia frutescens (SF) on the bioavailability of atazanavir (ATV) in twelve healthy male subjects. During Phase I (Day 1), subjects ingested a single dose of ATV and blood samples were drawn before dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 9.0, 12, 18, and 24 hours after dose. From Day 3 to Day 14, a single dose of milled SF was administered twice daily to each subject. During Phase II, Day 15, subjects ingested single doses of ATV and SF. Blood samples were drawn as previously described. Plasma was harvested from blood samples and the concentration of ATV therein was determined. For each phase, the mean ATV plasma concentration-time profile was plotted and the means of AUC0-24 and C max for ATV were computed. The geometric mean ratios and confidence intervals (CIs) for C max and AUC0-24 hr were 0.783 (0.609-1.00) and 0.801 (0.634-1.01), respectively. The CIs for both PK parameters fell below the limits of the "no-effect" boundary, set at 0.8-1.25, indicating that SF significantly reduced the bioavailability of ATV. This may potentially result in subtherapeutic plasma concentrations and thus reduced anti-HIV efficacy of ATV.

In Africa, *Sutherlandia frutescens* is a popular medicinal herb widely consumed by people living with human immunodeficiency virus/AIDS. Concomitant use with antiretroviral drugs has generated concerns of herb-drug interaction (HDI). The study by Fasinu, et al (2013, investigated the inhibitory effects of the crude extracts of *S. frutescens* on the major cytochrome P450 isozymes with the use of pooled human liver microsomes. Its effect on the metabolic clearance of midazolam using cryopreserved hepatocytes was also monitored. The potential of *S. frutescens* to inhibit human ATP-binding cassette transporters (P-gp and BCRP) and the human organic anion transporting polypeptide (OATP1B1 and OATP1B3) activity was assessed using cell lines overexpressing the transporter proteins. *S. frutescens* showed inhibitory potency for CYP1A2 (IC(50) = 41.0 µg/ml), CYP2A6 (IC(50) = 160 µg/ml), CYP2B6 (IC(50) = 20.0 µg/ml), CYP2C8 (IC(50) = 22.4 µg/ml), CYP2C9 (IC(50) = 23.0 µg/ml), CYP2C19 (IC(50) = 35.9 µg/ml), and CYP3A4/5 (IC(50) = 17.5 µg/ml [with midazolam1'-hydroxylation]; IC(50) = 28.3 µg/ml [with testosterone 6β-hydroxylation]). Time-dependent (irreversible) inhibition by *S. frutescens* was observed for CYP3A4/5 (K(I) = 296 µg/ml, k(inact) = 0.063 min(-1)) under the conditions of this study. *S. frutescens* also delays the production of midazolam metabolites in the hepatocytes, decreasing its clearance by 40%. Furthermore, *S. frutescens* inhibited P-gp (IC(50) = 324.8 µg/ml), OATP1B1 (IC(50) = 10.4 µg/ml), and OATP1B3 (IC(50) = 6.6 µg/ml). The result indicates the potential for HDI between *S. frutescens* and the substrates of the affected enzymes, if sufficient *in vivo* concentration of the extract is attained.

Jiang, *et al.* (2014) were of the opinion that previous studies on *S. furtenscens* (SF) mainly focused on physiological effects of SF on cellular and systemic abnormalities associated with these diseases, while little was known about its effects in the brain and immune cells in the central nervous system. Results of their study indicated that ethanol extracts of SF (SF-E) suppressed NMDA-induced reactive oxygen species (ROS) production in neurons, and LPS- and IFNγ-induced ROS and nitric oxide (NO) production in microglial cells. SF-E's action on microglial cells appeared to be mediated through inhibition of the IFNγ-induced p-ERK1/2 signalling pathway which is central to regulating a number of intracellular metabolic processes including enhancing STAT1α phosphorylation and filopodia formation. The involvement of SF in these pathways suggests the potential for novel therapeutics for stress and prevention, and/or treatment of HIV/AIDS as well as other inflammatory diseases in the brain.

According to Africa & smith (2015), it is common practice for HIV+ individuals in developing countries to make use of traditional medicines. One such medicine is *S. frutescens* - commonly consumed as a water infusion. They investigated the efficacy of *S. frutescens* as an anti-inflammatory modality in an in vitro co-culture model of the blood-brain barrier (BBB) in this context and found that their results caution against the use of *S.frutescens* as anti-inflammatory modality at any stage post-HIV infection.

Zonyane, S., Fawole, O.A., la Grange, C., Stander, M.A., Opara, U.L. & Makunga, N.P. 2020.
"Extracts of *Sutherlandia frutescens* (cancer bush) exhibit considerable qualitative and quantitative chemical variability depending on their natural wild origins. The purpose of this study was thus to determine bioactivity of extracts from different regions using in vitro antioxidant and anti-cancer assays. Extracts of the species are complex and are predominantly composed of a species-specific set of triterpene saponins (cycloartanol glycosides), the sutherlandiosides, and flavonoids (quercetin and kaempferol glycosides), the sutherlandins. For the Folin-Ciocalteu phenolics test values of 93.311 to 125.330 mg GAE/g DE were obtained. The flavonoids ranged from 54.831 to 66.073 mg CE/g DE using the aluminum chloride assay. Extracts from different sites were also assayed using the 2,2-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$) radical scavenging method and ferric reducing anti-oxidant power (FRAP) methods. This was followed by an in vitro Cell Titer-Glo viability assay of various ecotypes using the DLD-1 colon cancer cell line. All test extracts displayed anti-oxidant activity through the $DPPH^{\bullet}$ radical scavenging mechanism, with IC_{50} values ranging from 3.171 to 7.707 $\mu g \cdot mL^{-1}$. However, the degree of anti-oxidant effects differed on a chemotypic basis with coastal plants from Gansbaai and Pearly Beach (Western Cape) exhibiting superior activity whereas the Victoria West inland group from the Northern Cape, consistently showed the weakest anti-oxidant activity for both the $DPPH^{\bullet}$ and FRAP methods. All extracts showed cytotoxicity on DLD-1 colon cancer cells at the test concentration of 200 $\mu g \cdot mL^{-1}$ but *Sutherlandia* plants from Colesburg (Northern Cape) exhibited the highest anti-cancer activity. These findings confirm that *S. frutescens* specimens display variability in their bioactive capacities based on their natural location, illustrating the importance of choosing relevant ecotypes for medicinal purposes."

Isoniazid

In a study by Wilson, *et al*. (2015), they found that possible interaction between *S. frutescens* and isoniazid preventive therapy (IPT) needs further evaluation, and may presage antagonistic interactions with other herbs having similar biochemical (antioxidant) properties. They identified no other safety issues relating to consumption of *S. frutescens* in their cohort.

Stress, Anxiety and Hpertension

Because *S. frutescens*, a traditional African medicinal plant, was said to be used by certain groups for the treatment of stress and anxiety, Seargent, *et al*. (2017) in their study, aimed at linking anti-stress and anti-inflammatory properties of *S. frutescens* to its influence on glucocorticoid biosynthesis and the inflammatory response via steroid receptor interaction. Their data provided evidence linking anti-stress, anti-inflammatory and anti-hypertensive properties of *S. frutescens* to inhibition of steroidogenic enzymes and modulation of adrenal hormone biosynthesis. They concluded that their findings suggest *S. frutescens* and SUB (sutherlandioside B) exhibit dissociated glucocorticoid characteristics which underline potential therapeutic applications in the treatment of inflammation and hypertension.

Cell Death (Apoptosis)

Oesophageal cancer is the ninth most common cancer in the world and the second most common cancer among South African men. It also has one of the lowest possibilities of cure, with the 5-year survival rate

estimated to be only 10% overall. Sutherlandia frutescens, or the "cancer bush", is a medicinal plant indigenous to southern Africa that is believed to have anti-cancer and anti-proliferative properties. The aim of a study by Skerman, Joubert & Cronjé (2011) was to investigate the potential apoptosis-inducing effects of two *S. frutescens* extracts and one *Sutherlandia tomentosa* extract on the SNO oesophageal cancer cell line. Time- and dose-response studies were conducted to establish treatment conditions of 2.5 and 5mg/ml of crude plant extracts. Microscopy studies revealed that S. frutescens- and S. tomentosa-treated SNO cells had morphological features characteristic of apoptosis. Annexin V/propidium iodide flow cytometry confirmed that the extracts do, in fact, induce apoptosis in the SNO cells. Caspase inhibition studies seem to indicate that extracts A (S. frutescens (L.) R. Br. subsp. microphylla from Colesberg), B (S. frutescens (L.) R. Br. subsp. microphylla from Platvlei) and C (S. tomentosa Eckl. & Zeyh from Stil Bay) are able to induce caspase-dependent as well as -independent cell death. The S. frutescens and S. tomentosa extracts were found to be more cytotoxic to cancerous SNO cells when compared to the PBMCs. The researchers concluded that *S. frutescens* and *S. tomentosa* extracts show promise as apoptosis-inducing anti-cancer agents.

Sutherlandia frutescens (SF), a popular traditional medicinal plant found in various parts of southern Africa, is used for treatment or management of HIV/AIDS and other diseases including cancer. However, its toxicity profile has not been fully established. The aims of a study by Ngcobo, *et al*. (2011) were to examine the effects of 70% ethanol (SFE) and deionised water (SFW) extracts on normal isolated human T cells. An experimental study on normal human lymphocytes treated with doses SF extract doses ranging from 0.25 to 2.5 mg/ml. Untreated, vehicle-treated (Ethanol) and camptothecin (CPT) treated normal T cells were used as controls. Induction of cell death, changes in intracellular ATP, caspase-3/-7 activity and nuclear changes were analysed using flow cytometry, luminometry and nuclear staining (Hoechst) respectively. The highest concentration (2.5 mg/ml) of SFE extract induced significant necrosis (95%), depletion of ATP (76%), and inhibition of caspase-3/-7 activity (11%) following a 24 hour incubation period ($p < 0.001$). The 2.5 mg/ml concentration of SFW showed the same trend but were less effective (necrosis- 26%, ATP- 91%, & caspase-3/-7- 15%). These effects showed a time-dependence over 48 hours of incubation, with high doses of SFE extracts eliminating viable cells by necrosis, depleting ATP levels and decreasing caspase-3/-7 activity ($p < 0.001$). The activity of SFE extract was independent of ethanol. The SFW extract dilutions were less toxic than the SFE extracts. Significant DNA fragmentation as demonstrated by Hoechst staining was also seen over 48-hour incubation for high doses of both types of SF extracts. Their results showed that although high concentrations of SF extracts could be toxic to normal T cells *in vitro*, SFW fractions were relatively safe for use.

The scientific study of natural products traditionally used in anticancer preparations has yielded several therapeutically relevant compounds. One of these traditional preparations with potentially beneficial properties is aqueous extracts of *Sutherlandia frutescens*, a shrub indigenous to the Western Cape region of South Africa. The aims of a study by Vorster, Stander & Joubert (2012) were to evaluate *in vitro* efficacy of these preparations on the MCF-7 breast adenocarcinoma and MCF-12A non-tumorigenic cell lines in terms of cell proliferation, cell morphology and possible induction of cell death. Crystal violet staining was used to evaluate cell proliferation, light-and fluorescence microscopy were used to investigate both intracellular and extracellular morphological features of apoptosis and autophagy (e.g. membrane blebbing, condensed chromatin and intracellular lysosomes), while flow cytometry quantified cell cycle changes and induction of apoptosis through analysis of the flip-flop translocation of phosphatidylserine. The results of their study indicated that crystal violet staining showed a time- and dose specific response to aqueous *S. frutescens* extracts, revealing exposure to 1mg/ml aqueous extract for 48h to be ideal for comparing the differential effects of *S. frutescens* in the MCF-7 and MCF-12A cell lines. Microscopy showed distinct morphological changes with hallmarks of apoptosis being observed in both cell lines. Flow cytometry revealed a decrease in actively cycling cells in both cell lines, and a 4.36% increase in phosphatidylserine translocation in the MCF-7 cell line, indicative of apoptosis induction, while fluorescence microscopy showed

evidence of the induction of autophagy. Their analyses revealed the carcinogenic MCF-7 cell line to be more susceptible to the cytostatic and cytotoxic effects of aqueous extracts of *S. frutescens* when compared to the non-tumorigenic MCF-12A cell line, thus warranting further research into the exact cellular mechanisms involved and the possible synergistic activities of *S. frutescens* ingredients.

S. frutescens has traditionally been used for the treatment of various ailments, although it is best known for its claims of activity against cancers. The aim of a study by van der Walt, Zakeri and Cronjé (2016) was to investigate whether an extract of *S. frutescens* could induce apoptosis in the A375 melanoma cell line and to outline the basic mechanism of action. *S. frutescens* extract induced apoptosis in A375 cells as evidenced by morphological features of apoptosis, phosphatidylserine exposure, nuclear condensation, caspase activation, and the release of cytochrome c from the mitochondria. Studies in the presence of a pan-caspase inhibitor alluded to caspase-independent cell death, which appeared to be mediated by the apoptosis inducing factor. Taken together, the results of this study showed that *S. frutescens* extract is effective in inducing apoptosis in malignant melanoma cells and indicates that further *in vivo* mechanistic studies may be warranted.

Prostate Cancer Cells

In a study by Lu, et al. (2015), the researchers hypothesized Sutherlandia might act through Gli/Hedgehog (Hh)-signaling in prostate cancer cells and used RNA-Seq transcription profiling to profile gene expression in TRAMPC2 murine prostate cancer cells with or without Sutherlandia extracts. They found 50% of Hh-responsive genes could be repressed by Sutherlandia ethanol extract, including the canonical Hh-responsive genes Gli1 and Ptch1 as well as newly distinguished Hh-responsive genes Hsd11b1 and Penk.

In their study on Gli/Hedgehog prostate cancer cells, Lin, *et al*. (2016) found Sutherlandioside D was the most potent compound in the crude extract of *S. frutescens* that could suppress Gli-reporter in Shh Light II cells. Together, they state, there resarch suggests that the *S. frutescens* extract may exert anti-cancer effect by targeting Gli/Hh signaling, and Sutherlandioside D is one of the active compounds.

Immune Stimulation

Sutherlandia frutescens (SF) is one of the medicinal plants used as an immune booster in the treatment of chronic ailments such as HIV/AIDS and cancer. Limited data suggest that its efficacy is based on its regulatory effect on cytokines, the critical components of the immune response. In a study by Ngcobo, et al. (2012), they investigated the *in vitro* immunomodulatory effects of SF extracts on normal human peripheral blood mononuclear cells (PBMCs). An ELISA-based assay was used to assess the levels of expression of 12 cytokines in treated cells. An adenosine triphosphate (ATP) assay was used to assess cell viability in relation to cytokine secretion. SF ethanol extracts induced changes in cytokine secretion relative to the dose of the extract. Generally cytokine expression and secretion was low in concentration because were not stimulated with any endotoxin. The high SFE dose (2.5 mg/ml) significantly ($p<0.001$) decreased some cytokines including TNF-α and IL 1β. Low doses of this extract (0.5 mg/ml) did not change TNF-α and IL 1β secretion from the baseline (untreated cells). Changes in cytokine secretion of SFE treated cells tracked changes in ATP levels (cell viability). The SFW extract-induced changes in cytokine secretion were independent of cell viability. TNF-α was decreased ($p<0.001$) by the high dose of SFW extract while IL 1β and IFNγ were increased ($p<0.01$) by the same dose. High doses decreased cell viability which was reflected in cytokine secretion. It is evident, from the results, that SF extracts could modulate cytokine secretion in unstimulated normal PBMCs *in vitro*. The researchers recommended further studies in animal models to advance understanding of this immunomodulatory activity.

In a study aimed to investigate the potential immuno-stimulatory activity of a polysaccharide-enriched fraction (SFPS) from a decoction of S. frutescens, Lei, *et al*. (2015) demonstrated for the first time potent immune-stimulatory activity in a decoction prepared from *S. frutescens*. They believe that the immune stimulatory activity found was due, in part, to the action of polysaccharides present in the decoction that acts by way of TLR4 receptors and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway. These findings provide a plausible mechanism through which they could understand some of the medicinal properties of *S. frutescens*.

Oxidative Stress

Sutherlandia frutescens (L.) R.Br. (SF), a South African plant that is widely used to treat stress, infections, cancer, and chronic diseases, many of which involve oxidative stress. The aim of a study by Tobwala, et al. (2014) was to quantitatively assess the antioxidant potential of SF extracts in cell-free system as well as in cell lines. The results of their research indicated that: (1) SF extracts have significant antioxidant potential that is dependent upon the nature of the extraction solvent and (2) SFE protects against tBHP-induced oxidative stress in cells by scavenging ROS and preserving intracellular GSH/GSSG. They concluded that oxidative stress is implicated in a number of disorders, and due to the public's concerns about synthetic antioxidants, various natural antioxidants are being explored for their therapeutic potential. Their findings support claims for *S. frutescens* being a promising adjunctive therapeutic for oxidative stress-related health problems.

Psychological Stress

In their study (Smith & van Vuuren, 2014) manipulated a rodent model of acute psychological stress by acutely administering a low dose (4 mg/kg body mass) of *S. frutescens* extract 30 min prior to stress exposure (1 h restraint), to elucidate both its central and peripheral mechanisms of action in the context of acute stress. After 1 h of exposure to stress, acute restraint resulted in a significant increase in plasma corticosterone levels (56 ± 33 versus 499 ± 50 ng/ml; $P < 0.0001$) and anterior pituitary adrenocorticotropic hormone (ACTH) levels (0.066 ± 0.017 versus 0.202 ± 0.033% fluorescent area; $P = 0.07$), while decreasing hippocampal glucocorticoid receptor (GR) and gamma-aminobutyric acid (GABA)(A)α1 receptor levels (both $P < 0.05$). While the low dose of *S. frutescens* administered did not seem to have an effect on the down-stream stress response, it abolished the stress-induced down-regulation of GR, in a manner independent of GABA(A)α1 receptor. Results suggest a non-sedative effect of low-dose *S. frutescens* and points to central mechanisms of action that is in support of the anecdotal claims for its effectiveness as complimentary treatment in chronic stress-associated diseases.

Diabetes

The African medicinal plant *Sutherlandia frutescens* (L.) R.Br. (Fabaceae) is known to be traditionally used to treat diabetes and has been shown to have anti-diabetic properties in animal models. In a study by Williams, *et al.* (2013), they investigated the capacity of an aqueous extract of *Sutherlandia frutescens* to prevent insulin resistance (a precursor of type 2 diabetes) in a human liver cell culture and to identify genes regulated by *Sutherlandia frutescens* treatment. The results of their study showed that the insulin resistant Chang liver cells took up significantly less 2-[(3)H]-deoxyglucose ($p<0.05$) than controls, released more glucose into the culture medium ($p<0.05$) and accumulated more intracellular lipid ($p<0.05$). Simultaneous treatment with *S. frutescens* prevented development of these insulin resistance parameters ($p<0.05$). A total of 27 potential gene targets of *S. frutescens* were significantly up or down regulated in the *S. frutescens* treated insulin resistant cells. The gene VAMP3, which plays a role in vesicle transport, were down-regulated by insulin resistance, and up-regulated by *S. frutescens*. Twenty six other genes encoding

vesicle transporters, receptors, signalling molecules, transcription factors, and metabolic enzymes were significantly regulated by *S. frutescens*. Their results confirmed that *S. frutescens* could prevent insulin resistance in hepatocytes. The identified changes in gene expression indicated several potential mechanisms of anti-diabetic action for *S. frutescens*, reflecting the multiple bioactive compounds previously identified in aqueous extracts of *S. frutescens*.

Lipid Metabolism

High fat diet induced insulin resistance correlates with dyslipidaemia and ectopic fat deposits in skeletal muscle and liver. The effects of *Sutherlandia frutescens*, an antidiabetic medicinal plant, on lipid metabolism were evaluated by MacKenzie, *et al*. (2012) in an insulin resistant (IR) rat model and in 3 T3-preadipocytes. Wistar rats received normal diet (ND) or high fat diet (HFD). After the onset of IR in the HFD group, the rats were subdivided into two subgroups, which either continued with HFD or were treated with 50 mg *S. frutescens*/kg BW/day and HFD (HFD + SF). After 4 weeks, the HFD + SF rats had a significantly lower body weight than the HFD rats ($p < 0.05$). Blood plasma analysis showed a decrease in insulin, free fatty acids and triglycerides. Related changes in lipid parameters were observed in the liver, skeletal muscle and adipose tissue. To investigate the effects of *S. frutescens* on adipose tissue, 3 T3-L1 cells were used as a model. Treatment with *S. frutescens* led to a decrease in triglyceride accumulation, whilst glucose consumption and lactate production were increased ($p < 0.05$). The results indicated that *S. frutescens* directly affected mitochondrial activity and lipid biosynthesis in adipose tissue and provide a mechanism by which *S. frutescens* can restore insulin sensitivity by modulating fatty acid biosynthesis.

Drug-herb Interaction

Sutherlandia frutescens (Sutherlandia), an African herbal supplement was recommended by the South African Ministry of Health for the treatment of AIDS patients. However, no reports yet existed delineating the effect of *Sutherlandia* on pharmacokinetics of antiretroviral agents. Therefore, an investigation was conducted by Minocha, *et al*. (2011), aimed at screening the effects of short term and chronic exposure of *Sutherlandia* on oral bioavailability and pharmacokinetics of nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor, in Sprague Dawley rats. NVP (6 mg/kg) was administered orally alone (control) and with co-administration of S*utherlandia*; short term (12 mg/kg single dose) and long term (12 mg/kg, once a day for 5 days). No significant difference in the pharmacokinetic parameters of NVP was found upon short-term co-administration of *Sutherlandia*. However, there was a 50% decrease ($p<0.05$) in the AUC and C(max) values of NVP after 5 days of chronic exposure with *Sutherlandia*. In addition, quantitative RT-PCR studies demonstrated a 2-3-fold increase in the hepatic and intestinal mRNA expression of CYP3A2, relative to vehicle control. To further confirm, if this could translate into a clinically relevant pharmacokinetic interaction in patients, we tested this hypothesis employing LS-180 cells as an in vitro induction model for human CYP3A4. Ninety-six hours post treatment, similar to positive control rifampicin (25 µM), S*utherlandia* extract (300 µg/mL) resulted in elevated m-RNA expression levels and functional activity of CYP3A4 (human homologue of rodent CYP3A2) in LS-180 cells. Taken together, their results suggest that a potential drug-herb interaction is possible when NVP is co-administered with *S. frutescens*, although this hypothesis still remains to be investigated in a clinical setting.

Claimed Medicinal Uses of Sutherlandia Frutescens

According to Aboyade, et al. (2014) *Sutherlandia frutescens* is used in South Africa by an array of healers, such as herbalists (*inyanga*), diviners (*isangoma*), bush doctors (*bossiedokters*), Rastafarians, alternative and allopathic medicine practitioners, and lay people. 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 frutescens* is used to wash wounds and the eyes and to reduce fevers, and the infusions from the leaves and stems are used to treat various ailments.

The following medicinal claims have been made regarding Sutherlandia frutescens:

- Pyrexia (fever)
- Depression and stress
- Cancer
- Improvement of quality of life in cancer, HIV/Aids and Tuberculosis
- As at tonic
- 'Purification' of blood and wounds
- Skin conditions and inflammation
- Diabetes
- Kidney and liver conditions
- Rheumatism
- Stomach complaints
- Peptic ulcer
- Dysentery
- Gastritis
- Heartburn
- Reflux oesophagitis
- Enhance appetite and prevention of wasting
- Emesis (induce vomiting)
- Colds and influenza
- Chronic bronchitis
- Haemorrhoids
- Urinary tract infections
- Back pain
- Gonorrhoea
- Cystitis
- Prevention and treatment of asthma
- Gout
- Rheumatoid arthritis
- Immune booster
- Chicken pox
- Heart failure

Dwarka, D., Agoni, C., Mellem, J.J., Soliman, M.E. & Baijnath, H. 2020.
"The coronavirus is a group of viruses found in animals as well as humans and have been detected since the 1960s. However, a newly identified form, SARS-CoV-2, has triggered a recent pandemic of respiratory disease now called COVID-19. There is currently no specific antiviral drug for the treatment of this pandemic, with most treatment strategies focused on symptomatic management and supportive therapy. As such, several drug discovery efforts are ongoing for potent treatment agents, with medicinal plants gradually gaining prominence. Approximately 80% of the South African population use traditional medicines to meet their primary health care needs. The current study aimed to identify potential COVID-19 therapeutic agents from a list of 29 bioactive compounds isolated from commonly used South African medicinal plants using molecular docking and molecular dynamics. Molecular docking identified arabic acid from *Acacia senegal* and L-canavanine found in *Sutherlandia frutescens* as a potential inhibitor of SARS-CoV-2 3C-like

main protease. Similarly, hypoxoside isolated from *Hypoxis hemerocallidea* and uzarin from *Xysmalobium undulatum*, were identified as a potential inhibitor of SARS-CoV-2 receptor binding domain and SARS-CoV-2 RNA-dependent polymerase. These four bioactive compounds exhibited favourable binding orientations characterized by strong molecular interactions within respective inhibitors binding pockets of the target enzymes. Molecular dynamics simulations revealed that the binding of the identified inhibitors are characterized by structural perturbations which favour the inhibitory potency of these bioactive compounds. Additionally, *in silico* pharmacokinetic assessment of the compounds demonstrated favourable anti-SARS-CoV-2 properties. Although not conclusive, further experimental exploration of these compounds could serve as a starting point for the discovery of novel SARS-CoV-2 therapeutic."

Position of the Cancer Association of South Africa (CANSA)

The Cancer Association of South Africa (CANSA) recognises the availability of various dosage forms of *Sutherlandia frutescens* in shops, pharmacies, herbal shops and/or from traditional medicine suppliers (traditional healers).

CANSA wishes to confirm its position:

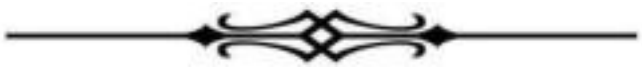
- That any individual who is unsure whether he/she may have one or other form of cancer, must refrain from using any traditional and/or over-the-counter medication without having consulted a health professional.

- That any individual who has been diagnosed with one or other form of cancer, must refrain from using any traditional and/or over-the-counter medication without having informed his/her treating physician or prior to having consulted a health professional.

Medical Disclaimer

This Fact Sheet and Position Statement is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet and Position Statement.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet and Position Statement, neither it, nor any contributor(s) to this Fact Sheet and Position Statement can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet and Position Statement.



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