CANAVANINE TOXICITY: IS SUTHERLANDIA A HEALTHY HERB OR POTENT(IAL) POISON?

HIV POSITIVES AND AIDS SUFFERERS BEWARE: THE REMEDY MAY BE WORSE THAN THE ALLEGED DISEASE

By Stuart Thomson, Director, Gaia Research Institute. <director@gaiaresearch.co.za> January 2002

Sutherlandia frutescens, an indigenous Southern African shrub commonly known as the "cancer bush / kankerbos" has a long traditional African and settler folklore medicinal history, but has recently been hyped by a band of ethno-pirates (those exploiting the traditional culture and intellectual property of indigenous people for financial gain) as a treatment, but usually not a cure, for cancer and AIDS, an action which is specifically forbidden by law, for the good reason that it may raise false hopes and even lead to substitution for effective treatment of a life-threatening illness.

There is absolutely no credible scientific support for the cancer claims *(Wicht J, S Afr Med Res, 16, 306, 1918); (Watt J & M Breyer-Brandwijk, The Medicinal and Poisonous Plants of Southern and Eastern Africa, E & S Livingstone, 1962); (C Smith (Ed), Common Names of South African Plants, Bot Surv Mem No 35, Govt Printer, 1966); (B-E van Wyk, B van Oudtshoorn, N Gericke, Medicinal Plants of South Africa, Briza Publications, 1997)*. There is likewise no credible scientific support for the new AIDS treatment claims. There is however, considerable evidence of a slow insidious poisoning, resulting in severe, even life-threatening toxicity, as attested to hereunder.

The callous businessmen making these claims, as well as the reporters and vendors repeating them, are socially and criminally irresponsible in the extreme. The company responsible for this scam is 'Phyto Nova' Development CC and its members, Nigel Gericke, Carl Albrecht, Ben-Erik van Wyk and Bani Isaac Mayeng, have long used taxpayer's money allocated to the Rand Afrikaans University and universities of Stellenbosch, Cape Town and Western Cape to advantage themselves and prejudice traditional healers in a selfish private money-making scam.

The hype rides on the back of a masters thesis by a student of Albrecht at the University of Stellenbosch and later, chemical analysis of the plant by van Wyk at RAU, which revealed two abundant chemicals: Canavanine and Pinitol (plus some GABA), which former two had previously been patented as medicinal agents. Propaganda duty falls to Gericke, a medical doctor, formerly with SA Druggists and one of the founders of the ethno-pirate Tramed project, along with past Medicines Control Council (MCC) chairman, Peter Folb at UCT. The fourth Phyto Nova member is Mayeng, also with Tramed, later with current MCC chairman Peter Eagles at UWC and recently with an even greater conflict of interest, as medicines control officer in charge of complementary medicines with the MCC.

Sutherlandia is by no means the only source of these identified secondary metabolites (having no essential role in the plant's primary metabolism, but having defensive roles against herbivorous predation). Several legumes, often the whole plant, but in particular the seeds, contain the known toxic chemical canavanine, the most notorious being the jack bean (Canavalia), but even alfalfa sprouts have been implicated in significant human toxicity. Pinitol on the other hand, is a relatively innocuous chemical, widely present in many foods, especially legumes, including soya, chickpeas, alfalfa and clover, and commercially extracted from Bougainvillea, pine, redwood and jojoba seed meal.

Stripped of its pretence at exclusivity (bar for one doubtful novel molecule – most plants have several) and seriously limited by the relative concentrations of the toxic canavanine constituent, Sutherlandia is devoid of any safe long-term benefit, since eventually, even at minimal therapeutic doses, its cumulative delayed immunotoxicity will predominate over its early antimicrobial and anti-inflammatory properties, leading to serious disease states, as the arginine analog increasingly enfolds into the victims protein and their immune systems eventually turn on themselves. Of concern is that the old trick of terminating any safety studies at just that toxic juncture, is likely. The true risk/benefit ratio for the chronic use recommended by Phyto Nova for AIDS and cancer is clearly negative. Dosage is likely to be either too high for safety, or too low for sustained beneficial effect, either too risky or useless. Of course, the placebo effect is likely to be high given the type of person likely to resort to the use of such products.

The media have reported that the South African Medical Research Council is to conduct safety and partial efficacy trials with Sutherlandia. Gilbert Matsabisa, a UCT doctor involved in Folb's ethnopiracy Tramed project (now the SA Traditional Medicines Research Unit) and a long-time associate of Phyto Nova members Gericke and Mayeng, was recently appointed MRC manager of Indigenous Knowledge Systems Initiative and is using his influence to abuse taxpayer's funds to conduct studies that clearly should have been conducted by Phyto Nova themselves, well prior to marketing their products. Mayeng, who would have used his position at the MCC to gain approval for subsequent clinical trials, was recently "shifted" due to sustained PHARMAPACT protests. Credo Mutwa, a respected traditional healer, was tricked into promoting Sutherlandia amongst the traditional African healers. Bioharmony, a shady operation peddling several questionable medicines and involved in several scandals over non-credentialed staff posing as registered practitioners, is the local health shop distributor. Discom stores will retail products of further questionable quality made by Impilo Drugs to the lower class buyers at the greatest risk of toxicity. Vitalink peddles the products via an internet online health store. Internationally the drug-dealing honours go to the impressive sounding Biogenesis Laboratories, which not unsurprisingly comprises of no laboratories at all.

Of further concern are several illegal amateur clinical trials on human beings both within and without of our borders. Initiated by a Phyto Nova press release, the BBC's Carolyn Dempster reported on 30 November 2001, that Anne Hutchings, an ethno-botanist and lecturer at the University of Zululand was administering Sutherlandia to AIDS patients who attend a weekly clinic at Ngwelezane Hospital. Dempster also reported that Gericke had said that they were anecdotally accumulating evidence that wasted patients with AIDS, TB and cancer to which Sutherlandia was administered with a balanced food diet (not received before, nor controlled for), pick up weight, regain energy and appetite (as is to be expected with a previously unfed balanced diet). Also initiated by a Phyto Nova press release, Health-E's Kerry Cullinan reported on 30 November, that a medical doctor, Colleen Coetzee, who works for a large development Bank in KwaZulu-Natal has given Sutherlandia to over 600 employees and clients, claiming weight gain and reduction of "some" fungal and bacterial diseases. I am appalled at the lack of thoroughness with which Sutherlandia has been investigated for toxicity prior to mass marketing. Sunday Argus' Alex Smith, on 2 December 2001, quotes Gericke waxing lyrical, that the plant is *"a portfolio of beautiful elements"*. New Scientist's Gaia Vince reported on 30 November that Matsabisa, when queried about the possible hoped for approval of a clinical trial, stated that: *"The fact is that people are already using it and will continue whether or not the government approves trials"*. Michelle Galloway, MRC journalist stated: *"In the remote rural regions, MRC researchers are launching small trials of Sutherlandia among young women, the highest risk group for HIV infection, reports Janet Frohlich, MRC research site manager at Hlabisa"*. Unauthorised clinical trials on ignorant persons is not only unethical, but also unlawful and the perpetrators and their accomplices must be brought to book and any victims whose health has been harmed thereby, must be fully and appropriately compensated for all harm incurred to their health. The problem however, is that the disease states caused by chronic use of canavanine so closely resemble that of AIDS.

Some African countries with less stringent laws and ethical standards are also being used to test Sutherlandia. The Sunday Times' Jessica Bezuidenhout reported on 16 December 2001 that: "South African scientists struck a secret deal with the makers of the banned Aids "cure" Virodene, to use an unregistered herbal tablet on HIV-positive patients in 12 African countries. This revelation comes only three months after Virodene researchers were kicked out of Tanzania for illegally importing and testing their discredited anti-Aids drug on civilians and soldiers there. South Africa's Medicines Control Council was shocked to learn about the deal and plans to investigate the tablet (according to) MCC chairman Professor Eagles. An application for permission to conduct a clinical trial (only, for the first time) comes before the MCC in January. Phyto Nova's Dr Carl Albrecht said*: "We were not comfortable dealing with these people, but we were a fledgling company and it was a substantial order."* The deal fell through in June when the Virodene group defaulted on payment. The Sunday Times collected 60 of the tablets in Tanzania. The bottle was labeled as PO59. Virodene PO58 made world headlines in January 1997 when Dr Olga Visser made startling claims that her wonder drug could cure Aids. It was later found to contain a toxic industrial solvent that can cause fatal liver damage. It has been banned from use on humans in South Africa and internationally."

Ironically, SAPA, 14 Mar 2001 quoted Gericke as stating: *"The last thing South Africa needs is another Virodene"*.

PINITOL

Phyto Nova Development CC members claim Sutherlandia to be partially efficacious due to its rich pinitol content. They claim it to be a known anti-diabetic agent, which is used in the US to treat the wasting in cancer and AIDS patients. The single reference to the wasting treatment however refers to a patent, but is not supported by any published research whatsoever. The single reference to anti-diabetic treatment is archaic. Subsequent work has been limited to animal models and cultured cells and has not been supported by subsequent human studies, the only published human study being non-definitive, with pinitol performing no better than placebo in improving the actions of insulin in carbohydrate or fat metabolism *(Almada A, Nutrition Science News, Feb 2001)*, the authors of the study concluding that: "four weeks of oral pinitol supplementation did not alter basal glucose and lipid kinetics or the effect of insulin on glucose and lipid metabolism" *(Davis A, et al, Diabetes Care, 23(7), 2000)*.

Of concern however, is the suggestion of prolonged use of pinitol or pinitol-containing Sutherlandia for cancer and especially for AIDS, due to the fact that Klebsielleae and other Enterobacteria, including Yersinia, Erwinia and Salmonella, are reportedly capable of metabolizing pinitol and using it as a source of carbon and energy *(Talbot H & Seilder R, Appl Environ Microbiol, 37(5), 1979); (Talbot H & Seilder R, Appl Environ Microbiol, 38(4), 1979)*. Of particular concern is Klebsiella, strains of which, especially K pneumoniae, cause primary pneumonia, one of the main causes of death in AIDS, and also meningitis, and in infants, septicaemia. Many strains are now antibiotic resistant and cause serious infections, especially nosocomial- (hospital) and community-acquired, and particularly in infants and AIDS patients. *(Feldman C, et al, J Infect, 20(1), 1990); (Feldman C, et al, Respiration, 58(5-6), 1991); (Coovadia Y, et al, J Hosp Infect, 22(3), 1992); (Cotton M, et al, S Afr Med J, 81(2), 1992); (Adhikari M, et al, J Trop Pediatr, 41(2), 1995); (Furman A, et al, Clin Infect Dis, 22(1), 1996); (Donald P, J Trop Pediatr, 42(5), 1996); (Pitout J, et al, Antimicrob Agents Chemother, 42(6), 1998); (Leigh H, et al, Clin Ther, 22(7), 2000); (Nel E, J Trop Pediatr, 46(4), 2000); (Jeena P, et al, Ann Trop Paediatr, 21(3), 2001); (van De Wetering M, et al, Med Pediatr Oncol, 37(6), 2001); (O'Farrell N, Int J STD AIDS, 12(7), 2001); (Cotton M, et al, S Afr Med J, 91(2), 2001)*

GABA

Some Sutherlandia subspecies reportedly yield high concentrations of GABA, an inhibitory neurotransmitter assumed to account for the plant's folklore use for anxiety and stress. The seeds and leaves have been smoked by labourers and teenagers, leading some farmers to remove the plants from their land. *(B Erik van Wyk & N Gericke, People's Plants, Briza Publications, 2000)* Phyto Nova claims that Sutherlandia gives a profound sense of well-being. The desirability and legality of promoting Sutherlandia with such a claim, in addition to mood-improvement, and combating mental stress and as an anti-depressant for clinical depression and substance is also questionable.

SAFETY

This report will testify to the author having conducted and shared research that should have been undertaken by the companies involved and considered by them 'before' irresponsibly promoting their product without prior scientific safety testing and should accordingly accompany all marketing of Sutherlandia products so as to balance public information for and against its use and also form part of safety precautions that should from the outset have accompanied the product, considering its high chronic toxicity potential. This is a consideration that the various so-called scientists involved with Phyto Nova should collectively have undertaken, but it is evident that they have either not done their duties in this regard, or having done so, simply prioritised their business interests before public health and safety interests, which will further serve to bring the field of natural products publicly into disrepute.

This author's concerns are not intended to be malicious. They are well-founded and based on time-honoured public safety and toxicological principles. The principle that the expected benefit of a drug must outweigh its potential risk applies as much to traditional medicines as it does to synthetic drug preparations. No patient deserves to be treated with a remedy that is worse than the disease. It is essential that traditional medicines are also submitted to an appropriate benefit/risk analysis. *(De Smet P, J Pharmacol, 32(1-3), 1991)* Long-standing traditional experience may tell much about striking and predictable symptoms of acute toxicity, but it is a less reliable tool for the detection of reactions which are inconspicuous, develop gradually or have a prolonged latency period, or which occur uncommonly. Another reason why safety claims cannot always be based on traditional empiricism is that not all herbal remedies are firmly rooted in traditional medicine. *(De Smet P, Drug Safety, 13(2), 1995)*

Against the backdrop of a highly unlikely list of scientifically unsubstantiated beneficial properties and therapeutic claims, remains the issue of the safety of Sutherlandia for use for such purposes. It is grossly irresponsible, indeed criminally so, for the manufacturers and marketers of any drug, be it natural or otherwise, to promote its use to the desperate and gullible suffering populace 'before' formally establishing its long-term safety, as is clearly the case with Phyto Nova and Sutherlandia. There are now media reports of the Medical Research Council being asked to conduct formal safety and efficacy studies on Sutherlandia, but clearly these are the proprietary responsibility of Phyto Nova, should be conducted 'before' the sale of the product and should not rely on taxpayer's contributions.

The media however, unquestioningly perpetuate the safety myth, eg Rod McKenzie, Cape Times, 8 February 2001 states: *"Sutherlandia is regarded as a very safe herb"*. Also, Kerry Cullinan, Health-e News Service, 30 November 2001 states: *"Gericke says the plant is safe to use and no severe side effects have been reported"* (by the public guinea pigs – but no adverse drug reporting mechanisms are in place, yet some side-effects must be evident, to declare that they are not severe...yet), Gericke adding that*: "in the interest of public health, formal scientific safety studies are currently underway"*. On the same day, obviously following a Phyto Nova press release, Carolyn Dempster, BBC News, 30 November, 2001, in reference to Gericke, stated: *"having determined that the product was safe when administered with a balanced food diet* (rare in southern Africa)*, the company distributed Sutherlandia to Aids patients"*. How can the drug be declared safe and so promoted if it is yet to be formally tested?

Besides the media hype, readily fed by Phyto Nova, the company also makes several irresponsible and unsubstantiated safety claims on their website. Gericke states: *"In keeping with the World Health Organisation guidelines of the assessment of herbal medicines, Sutherlandia is generally regarded as safe on the basis of its long history of safe use in South Africa. No severe side-effects are known"*. This is clearly untrue, as shown below. The author of this report has published in a peer-reviewed science paper, the astonishing conservative estimate to the effect that 10-20, 000 South Africans are annually needlessly poisoned to death by traditional African medicines *(Popat A, et al, Clin Biochem, 43(3), 2001)*, which full paper is available at http://www.gaiaresearch.co.za/impila.pdf

Phyto Nova do suggest that Sutherlandia should not be used during pregnancy or breast-feeding, but do not inform the user why, though they do state in a recent publication that *"teratogenicity and abortions are known to have occurred" (B Erik van Wyk & N Gericke, People's Plants, Briza Publications, 2000)*. The manufacturers, distributors and especially the media however, with no apparent knowledge of its chronic toxic potential, are quick to hype up the claimed virtues of Sutherlandia, but rest assured, the cautionary contents of this report will be ignored, as witnessed by a 16 December, 2001 Sunday Times article, where the editor disallowed even a single precautionary to be mentioned in an article by Jessica Bezuidenhout, a research reporter who expressed interest in Sutherlandia/canavanine toxicity and was earlier provided with a fully referenced early draft version of this report.

CANAVANINE

The extensive use of plants as medicines has pointed out that herbal medicines are not as safe as frequently claimed. Instances of efficacy and toxicity have recently surfaced with several commercially available herbal medicines. It can be harmful to take herbal medicines without being aware of their potential adverse effects. Many plants produce toxic substances that discourage consumption by animals. Herbal preparations may come from plants that are not eaten by other animals, so it is not surprising that particular risks of toxicity are associated with the use of herbs that contain potentially toxic constituents. Herbal medicines can also be harmful if they delay or replace a more effective form of treatment, since many products are sold as dietary supplements but lack scientific information about their safe and effective use, because toxicological data and support of clinical studies is lacking. Both users and practitioners should be enabled to make the risk-benefit assessment before using any herbal medicine. Adverse effects that may occur with some herbal products include **systemic lupus erythematous syndrome**, due to the responsible constituent, L-canavanine. *(Capasso R, et al, Fitoterapia, 71:1001, 2000)*

Let us examine the immediately foregoing thesis as it pertains to canavanine-rich plants, in a loose chrono-subject order, abstracted directly from the published scientific literature so as to share various investigator's own perspectives on their research, as they pertain to the subject matter of the safety and efficacy of canavanine plants.

Nature's pesticides are one important subset of natural chemicals. Plants produce toxins to protect themselves against fungi, insects and animal predators. Many Leguminosae (now the Family: Fabaceae) contain canavanine, a toxic arginine analog that, after being eaten, is incorporated into protein in place of arginine. *(Ames B, et al, Dietary Pesticides, Proc Natl Acad Sci, USA, July 17, 1990)* Canavanine-rich plants have even been specifically investigated for their pesticidal properties *(Koul O, Phytoparasitica, 13(3-4), 1985); (Rosenthal G, J Chem Ecol, 12(5), 1986); (Rosenthal G, Dahlman D, Food Agric Food Chem, 39(5), 1991); (Rosenthal G, et al, J Agric Food Chem, 43(10), 1995); (Rosenthal G & Harper L, Insect Biochem Mol Biol, 26(4), 1996); (Rosenthal G, et al, J Agric Food Chem, 46(1), 1998)*. Canavanine is a potentially deleterious arginine antimetabolite whose toxicity is expressed in canavanine-sensitive organisms ranging from viruses to humans. *(Rosenthal G, et al, J Biol Chem, 264(23), 1989)* Many anti-nutritional and toxic factors abound in seeds, which are generally rich in nutrients and therefore more prone to attack from herbivores. These factors, including canavanine, defend plants against destruction and though good for the plant, cause deleterious effects or are even toxic to insects, animals and man. *(Makkar H & Becker K, Asian-Austral J Animal Sci, 12(3), 1999); (Siddhuraju P & Becker K, Nahrung, 45(4), 2001)*

Nonprotein amino acids in plants are often intermediates in the synthesis and catabolism of the protein amino acids and many of these amino acids may play roles as defensive agents. The best-characterized examples of nonprotein amino acids in plants are L-canavanine and L-canaline. Massive accumulation of canavanine, a structural analog of L-arginine, occurs in the seeds and leaves of many legumes, offering protection against predation. *(Nonprotein amino acids, Purdue University School Agriculture, undated)* Some herbivores, which are mixed feeders, have developed several survival defences of their own. A number of canavanine-degrading bacteria may break down sufficient of the dietary canavanine so that the toxic effects of this compound are reduced when ruminants eat canavanine-containing foods. *(Dominguez-Bello M, Stewart C, Syst Appl Microbiol, 13(4), 1990); (G Rosenthal & E Bell, in G Rosenthal & D Janzen (Eds), Herbivores: Their Interaction With Secondary Plant Metabolites, pp 353-386, Academic Press, 1979)* Some herbivores evade canavanine poisoning because their enzymes, like canavanine–producing plants, do not use canavanine by mistake *(W Purves, G Orians & H Hellar, Life: the Science of Biology, WH Freeman & Co, 1995)* Rodents, which are traditional seed-eaters, and the usual toxicological surrogate for humans, are fairly susceptible to canavanine poisoning, whilst primates and humans are least successfully adapted to the toxicity of canavanine in plants, as shall be attested to in the pages which follow.

In addition to the amino acids, which are the building blocks of proteins, living systems also produce nonprotein amino acids. These compounds possess a rich structural diversity and often elicit deleterious biological effects in viruses and all living systems *(Rosenthal GA. Q Rev Biol 52: 155, 1977); (G Rosenthal, Plant Nonprotein Amino and Amino Acids, Academic Press, San Diego, 1982)*. L-Canavanine, the L-2-amino-4- (guanidinoxy) butyric acid structural analog of L-arginine, is such a higher plant toxicant, produced and stored by leguminous plants, as part of their chemical defense, where it functions as a barrier against a wide array of insects and other pests *(G Rosenthal, in: Insecticides: Mechanism of Action and Resistance, D Otto & B Weber, (Eds), Intercept Ltd., 1982), (G Rosenthal, in: Frontiers and New Horizons in Amino Acid Research, K Takai, (Ed), Elsevier, 1992)*. [This data set is extracted from a much publicised cancer patent: *(Crooks P & G Rosenthal, Use of canavanine as a therapeutic agent for the treatment of pancreatic cancer, US Patent 5,552,440, 3 September 1996)*]

Based on toxicological data, **in terms of modern toxicology, canavanine is accordingly rated as "very toxic"**, **ie between extremely toxic and moderately toxic**, but relatively closer to the former than to the latter *(Rodricks J, Calculated Risks: The Toxicity and Human Health Risks of Chemicals in Our Environment, Cambridge University Press, 1992)*. This classification, however, does not take into consideration the irresponsibly suggested chronic use of canavanine by malnourished and/or already ill persons as commercially and media hyped with **Sutherlandia**.

The earliest toxicity reports were of observed effects in rats fed canavanine-containing meal *(Orru A, Cesaris-Demel V, Quanderni Nutrizone, 7, 273, 1941)*. Later experiments quantified the mammalian toxicity of canavanine, with 20mg/kg (body weight) having no effect, 200mg/kg showing clear damage and 2g/kg leading to death, all within 24hrs! When 1g/kg of arginine was fed together with 200mg/kg canavanine, no toxicity was observed. Boiling and ethanol extraction did not reduce toxicity. An explanation for the toxic effects was disturbance of protein metabolism related to disturbance of arginine functions. Lethal dose poisonings are only reached in exceptional cases. However, even small doses allow recognition of clear toxic effects. *(Tschiersch B, Pharmazie, 17, 621, 1962)* Relatively moderate canavanine feeding was observed to lead to a reduction in normal weight gain *(Jaffe W, Arnzie-mittle-Forsch, 10, 1012, 1960)*. Milk reduction was markedly reduced after feeding canavanine to dairy cows. When feed was given with protein-rich fodder, little ill-effects were noted. Canavanine is rapidly metabolized in the liver, yet damage is reported for this and other organs *(Shone D, Rhodesia Agric J, 58, 18, 1961)*.

Nuclear alterations in mammalian cell-induced by L-cananavine, were observed in quite early research *(Hare J, J Cell Physiol, 75:129, 1970)*. L-Canavanine, the guanidinooxy structural analog of L-arginine, can lead to the production of canavanine-containing proteins, which ultimately can disrupt critical reactions of RNA and DNA metabolism and protein synthesis. Canavanine also affects regulatory and catalytic reactions of arginine metabolism, arginine uptake, formation of structural components and other cellular processes. In these ways, canavanine alters essential biochemical reactions and becomes a potent antimetabolite of arginine. These deleterious properties of canavanine render it a highly toxic secondary plant constituent. *(Rosenthal G, Q Rev Biol, 52(2), 1977)* Canavanine, following prolonged administration, can result in toxic effects in various mammalian tissues. Some features of the deleterious effects of this compound are interference with the metabolism of the normal protein amino acids and involvement of specific tissues such as the liver. *(M Hegarty, Toxic amino acids of plant origin, in: R Keeler et al (Eds): Effects of poisonous plants on livestock. Academic, pp. 575-585, 1978); (Kay D, Crop and Product Digest No. 3 - Food legumes, Tropical Products Institute, pp 200-201, 1979)*

Post mortem of animals allowed to free range on canavanine-rich plants have revealed lesions and hemorrhages of the lymph glands *(M Clarke, D Harvey and D Humphreys, Veterinary Toxicology, Bailliere Tindall, p236, 1981)*. Canavanine has furthermore been determined to be a Vitamin B6 antagonist *(H Klosterman, in R Ory (Ed), Anti-nutrients and Natural Toxicants in Foods, Chap 16, 1981)*. The toxicity and pharmacokinetics of canavanine have been determined in laboratory rat studies. Twenty-one percent of the administered canavanine remained in the gastrointestinal tract 24 hr after an oral dose. Less than 1% was incorporated into the proteins of adult and neonatal rats 4 or 24 hr following administration. Repeated administration resulted in far greater uptake and more severe toxicity. Weight loss and alopecia were observed in rats given canavanine daily for 7 days. Food intake was decreased by 80% in adult rats subjected to this dosing regimen. *(Thomas D & Rosenthal G, Toxicol Appl Pharmacol, 91(395), 1987); (Thomas D & Rosenthal G, Toxicol Appl Pharmacol, 91(406), (1987)*

Besides the potential to cause a lupus erythematosus-like syndrome, general medical science and toxicological cautionary reports have been ongoing *(Shqueir A, et al, Anim Feed Sci Technol, 25(1-2), 1989); (J D'Mello, Toxic Amino Acids, in: J D'Mello, C Duffus & J Duffus (Eds), Toxic Substances in Crop Plants, Royal Soc Chem, pp 21-28, 1991); (Rosenthal G, Phytochem, 30(4), 1991); (Garcia-Bibao J, Alimentaria, 29(229), 1992); (J Chen, in A Tu, (Ed), Toxin-Related Diseases: Poisons Originating from Plants, Animals and Spoilage, Intercept Ltd, pp 55-99, 1993); (Gregory S, et al, Cell Immunol, 153(2), 1994); (Leporatti M, Fitoterapia, 67(6), 1996); (Rosenthal G & Nkomo P, Pharmaceut Biol, 38(1), 2000); (Tsirigotis M, et al, J Biol Chem, 276(49), 2001)*. In particular, the paradoxical effect of slightly increased lifespan (restricted only to high protein diets) but decreased reproduction due to teratogenic effects, have intrigued and concerned researchers *(Brown D, J Animal Sci, 72(Suppl 1), 1994); (Schardein J, J Toxicol Rev, 15(4), 1996); (Brown D, et al, J Nutr Immunol, 5(3), 1998)*. Studies evaluating cell aging in human diploid fibroblast cells however, have led to the lifespan being slightly shortened in canavanine-treated cells (as also with aspartame-treated cells) *(Kasamaki A, Urasawa S, J Toxicol Sci, 18(3), 1993)*.

The major toxicological concerns with canavanine-rich plants, as far as human poisoning is concerned, are immune system effects, particularly auto-immunity, where the body turns upon itself, via inappropriate oxidative free radical attack. A number of clinical reports and experimental studies have shown that autoimmune responses and/or autoimmune diseases and disorders are frequently chemically induced in humans by xenobiotics, including by canavanine *(Morimoto I, Kobe J Med Sci, 35(5-6), 1989); (Morimoto I, et al, Clin Immunol Immunopathol, 55(1), 1990); (Yoshida S & Gershwin M, Semin Arthritis Rheum, 22(6), 1993); (Bigazzi P, Toxicology, 119(1), 1997)*. Autoimmune disorders result from a breakdown of immunologic tolerance leading to an immune response against self-molecules. In most instances the events that initiate the immune response to self-molecules are unknown, but a number of studies suggest associations with environmental and genetic factors and certain types of infections. There have been associations of a number of xenobiotics with human autoimmune disease, including canavanine. Xenobiotics may also exacerbate an existing autoimmune disorder. *(Powell J, et al, Environ Health Perspectives, 107(Suppl 5), 1999); (Gebbers O, Schweiz Rundsch Med Prax, 90(44), 2001)*

The first signs of auto-immune problems in humans arose from observations that regular consumption of large quantities of canavanine-containing alfalfa seeds, often as sprouts, caused symptoms of toxicity. Amongst the first symptoms noted in humans was that of pancytopenia with splenomegaly *(Manilow M, et al, Lancet, 1, 615, 1981)*. Canavanine also induced certain hematologic and serologic abnormalities in monkeys test fed on alfalfa sprouts, causing a severe lupus erythematosus-like syndrome (SLE), which in man is characterised by a defect in the immune system, which is associated with anti-immunity, antinuclear antibodies, chromosome breaks and various other types of pathology. *(Manilow M, et al, Science, 216, 415, 1982)* The chromosome breaks appear to be due to oxygen radicals as they are prevented by superoxide dismutase *(Emerit I, et al, Hum Genet, 55, 341, 1980)*. The canavanine pathology was considered to be due, in part, to the production of oxygen radicals during phagocytization of antibody complexes with canavanine-containing protein *(Ames B, Science, 221, 4617, 1983)*. SLE has been exacerbated in humans and caused experimentally in monkeys through the regular ingestion of quantities of canavanine-containing alfalfa sprouts *(Roberts J, et al, (letter), N Engl J Med, 308, 1361, 1983)*.

The systemic lupus erythematosus (SLE) inducing property of alfalfa sprouts in monkeys has been attributed to their non-protein amino acid constituent, canavanine. Occurrence of autoimmune hemolytic anemia and exacerbation of SLE have been linked to ingestion of plant products containing canavanine. Researchers have reported the results of investigations into the effects of canavanine on T-cells. Canavanine has shown dose-related effects in vitro on human immunoregulatory cells, which could explain its SLE-inducing potential. These effects include: 1) diminution of the mitogenic response to both phytohemagglutinin and concanavalin A, as determined in both thymidine incorporation and cell cycle studies; and 2) abrogation of concanavalin A-induced suppressor cell function, which results in increased release of both IgG and DNA binding activity into supernatants by cells from normal subjects and SLE patients. These immunoregulatory effects of canavanine may explain the induction or exacerbation of SLE. *(Alcocer-Varela J, et al, Arthritis Rheum, 28(1), 1985)*

One report of a study of the effects in vitro and in vivo of canavanine on immune function in normal and autoimmune mice showed that Canavanine in high doses effectively blocks all DNA synthesis in vitro within 24 h. At lower doses, canavanine affected B-cell function of autoimmune mice, inhibiting [3H]thymidine incorporation in response to B-cell mitogens, and pokeweed-induced intracytoplasmic immunoglobulin synthesis, but stimulated intracytoplasmic immunoglobulin. The decrease in survival in canavanine-treated autoimmune mice correlated with an increase in spontaneous immunoglobulin-secreting cells (IgG greater than IgM) and antinuclear and double-stranded DNA antibodies. Histopathological analyses revealed increased glomerular damage and immunoglobulin deposition in the kidneys of the canavanine-treated autoimmune and normal mice. Ten percent of normal mice developed high titers of autoantibodies after 24 weeks of the diet. These data suggest that the dietary amino acid, canavanine, affects B-cell function resulting in autoimmune phenomena and providing a new animal model of autoimmunity, a diet-induced SLE syndrome. *(Prete P, Can J Physiol Pharmacol, 63(7), 1985)*

Professor Varro Tyler, a pharmacognosy authority at Purdue University, respected by both allopathic and complementary alternative medicine fraternities alike, warned that reports appeared noting that patients with clinically and serologically quiescent systemic lupus erythematosus (SLE) had even had the disease reactivated by ingesting canavanine-containing alfalfa tablets and he postulated that the canavanine present in all parts of the plant was replacing arginine in vital metabolic processes in the body, thus causing recurrence of SLE. *(Tyler V, et al, (Eds), Pharmacognosy, Lea and Febiger, 1988)* Reports on the alfalfa sprout / canavanine toxicity phenomenon were not restricted to the scientific press. By way of example, popular natural health author, Dr Andrew Weil, MD, of the University of Arizona, as a health columnist wrote that: “canavanine in alfalfa sprouts can harm the immune system, possibly ‘increasing’ the risk of cancer and degenerative diseases” *(Weil A, Are Sprouts Health Foods?: Naturally-occurring toxins create doubts, Natural Health, Nov/Dec, 1992)*. Many lay publications followed suite.

Systemic lupus erythematosus (SLE) in humans is characterized by a defect in the immune system that is associated with autoimmunity, antinuclear antibodies, chromosome breaks, and various types of *pathology (Ames B, et al, Proc. Natl. Acad. Sci. USA, July 17, 1990)*. Canavanine induced SLE is characterised by an auto-immune hemolytic anemia with low complement levels, positive antinuclear antibodies, anti-DNA, positive lupus cell preparations, and deposition of immunoglobulin and complement. *(D Metcalf, in: Food Allergy: adverse reactions to foods, D Metcalf, et al (Eds), Blackwell Scientific Publications, 1991); (A Mongey & E Hess, in D Wallace & B Hahn, Dubois’ Lupus Erythematosus and Associated Disorders, Lea and Febiger, 1993); (Herbert V, et al, Amer J Clin Nutr, 60: 639, 1994); (Brinker F, Herb Contraindications and Drug Interactions, Eclectic Medical Publications, pp 27-28, 1998); (Brown A, J Renal Nutr, 10(4), 2000)* **For anyone considering using a canavanine-containing product, eg Sutherlandia, for treatment of AIDS, consider that the SLE which it causes, often accompanies AIDS, is a complex disorder sharing similarities with AIDS as regards affecting a predominately young population, its propensity for multiple organ involvement and for causing potentially life-threatening episodes** *(Schattner A & Rager-Zisman B, Rev Inf Dis, 12:204, 1991); (Morrow W, et al, Clin Immunol Immunopathol, 58:163, 1991); (J Levy, HIV and the Pathogenesis of AIDS, ASM Press, 1998)*. (See Appendix 2)

Canavanine is a genotoxic mutagen in yeast cells, animals and humans, and is often used to induce and study mutagenesis in laboratory cultures and animals *(Morollo A, Ttroczi J, Environ Mutagen, 8(Suppl 6), 1986);* (Davies P & Parry J, Mol Gen Genet, 162(2), 1978); (Gocke E & Manney T, Genetics, 91(1), 1979); (McDougall K & Lemontt J, Mutat Res, 63(1), 1979); (Larimer F, et al, Mutat Res, 77(2), 1980); (Suiko M, et al, Daigaku Nogakubu, Kenkyu Hokoko, 29(2), 1982); (Bender E & Brendel M, Mutat Res, 197(1), 1988); (Fedorova I, et al, Genetika, 28(5), 1992); (Fedorova I, et al, Genetics, 148(3), 1998). The potential of canavanine to induce mutagenesis (and by implication, possibly cancer), intrigues researchers, who for example, using data in mathematical models which predict the stability of protein synthesizing systems, have found that if a single compound, eg the arginine analog canavanine, is discriminated very poorly from the cognate substrate, an "error catastrophe" must be envisaged *(Freist W, et al, J Theoret Biol, 193(1), 1998)*. Researchers have recently pointed out that while the negative effect of permanent contamination of populations because of spontaneous mutations does not appear to be very high for humans and animals when the environment was benign, a very different outcome was seen when environmental stress was induced in the laboratory, using canavanine *(Szafraniec K, et al, Proc Natl Acad Sci, 98(3), 2001)*.

Seeing as canavanine containing substances have been suggested as treatment for cancers, let us examine its potential in his regard directly from synopsis of the published works of a world authority on canavanine and cancer.

Canavanine is a potent arginine antimetabolite that bears strong structural analogy to its protein amino acid counterpart, arginine. As a subtle structural mimic of L-arginine, canavanine can function in all enzymic reactions for which arginine is a substrate. Therefore, canavanine potentially can inhibit any enzyme-directed reaction employing arginine as the preferred substrate. Canavanine assimilation can alter protein conformation and adversely affect normal biological function and biochemical activities. Exposure to canavanine adversely affects a basic property or functional parameter of one or more enzymes. Several studies of canavanine's antineoplastic activity have been conducted, demonstrating that canavanine could mediate its toxic effect not only at the level of protein function, but also through its ability to disrupt DNA replication. Canavanine's lethal effect was manifested preferentially in rapidly proliferating cells - a property essential to chemotherapeutic efficacy. These promising findings with canavanine had the drawback that canavanine's cumulative toxicity resulted in about a 15% diminution in body weight after 5 treatment days. Analysis of canavanine catabolism in the adult rat demonstrated that hepatic arginase fostered the hydrolysis of canavanine to yield L-canaline and urea; this reaction pathway was the principal basis for canavanine catabolism in this mammal. Thus, it is reasonable to propose that administration of L-canavanine to a human would result in the formation of L-canaline, a highly toxic nonprotein amino acid that is a powerful inhibitor of pyridoxal phosphate-dependent enzymes via a direct reaction between canaline and the vitamin B6 moiety of an enzyme. The intrinsic toxicity of canavanine is as a substrate for hepatic degradation via the action of arginine. Certain ester derivatives of canavanine (synthetic drug development) might provide an efficacious drug capable of eliciting little if any bodyweight loss while enhancing the therapeutic index for canavanine. *(Rosenthal G, L-canavanine: A Novel Chemotherapeutic Agent for Human Pancreatic Cancer, 2001)*

Canavanine has been shown to enhance human tumor cell killing in combination with radiation *(Green M & Ward J, Cancer Research, 43(9), 1983)*, but this finding has not led to any practical improvements in toxic radiation therapy. From another source, is a (limited result) report of an interesting L-arginine / L-canavanine comparative equivalent controlled study. Some guanidino compounds have been found to inhibit spontaneous mammary tumorigenesis in mice. Chronic treatment with Lilium auratum or Astragalus sinicus, which contains L-arginine or L-canavanine on spontaneous mammary tumorigenesis significantly inhibited the development but not the growth of mammary tumors, with no significant long-term deleterious side-effects with either product, estimating from body weight change and plasma component levels. These findings suggest that these natural products may act as prophylactic agents for mammary and possibly other types of tumors. *(Nagasawa H, et al, Anticancer Res, 21(4A), 2001)*

Please note that the implication arising from this last study abstract is that plant constituents other than canavanine are responsible for the positive effects, including simply L-arginine itself, for which L-canavanine is merely a mimic, which is mischievously substituted with positive, but potentially far more severe adverse-effects at any probable therapeutic (as opposed to prophylactic) doses. Consider briefly, research into arginine itself. Arginine is conditionally essential to most mammals and to humans. A high content is found only in high protein foods, with little in cereals and grains (but plenty in nuts). Arginine has been used to successfully treat depression (nitric oxide is synthesized from L-arginine) *(Yildiz F, et al, Psychopharmacology (Berl), 149(1), 2000)* and a variety of cancers *(R Braverman, with C Pfeiffer, et al, The Healing Nutrients Within: Facts, Findings and New Research on Amino Acids, Keats Publishing, 1997); (Takeda Y, et al, Cancer Res, 35, 390, 1975); (Critselis A, et al, Federat Proc, 36, 1163, 1977); (Pryme H, Cancer Lett, 5, 19, 1978); (Milner J, et al, J Nutr, 109, 489, 1979); (Barbul A, et al, Surg, 90(2), 1981); (Tayek J, et al, Clin Res, 33(1), 1985); (Reynolds J, et al, J Surg Res, 45, 513, 1988); (Reynolds J, et al, Surg, 104(2), 1988); (Park K, Proc Nutr Soc, 52:387, 1993); (Brittenden J, et al, Surgery, 115:205, 1994); (Ma, Q et al, World J Surg 20:1087, 1996); (Van Bokhorst-de van der Schueren M, et al Amer J Clin Nutr, 7(2), 2001).* Arginine enhances in vivo immune responses in mice *(Lewis B & Langkamp-Henken B, J Nutr, 130:1827, 2000)*.

In healthy adult humans, eight amino acids are indispensable (ie not synthesised in the body). Studies have revealed that that in certain nutritional or disease states or in certain stages of development, otherwise dispensable amino acids such as arginine may become indispensable and hence a classification has been proposed whereby the indispensability of amino acids be based on clinical and therapeutic considerations. *(Laidlaw S & Kopple J, Am J Clin Nutr, 46: 593, 1987)* Arginine is a precursor for three pathways, the products of which are involved in tissue injury and repair: nitric oxide, an effector molecule in inflammatory and immunological tissue injury; polyamines, required for DNA synthesis and cell growth; and proline, required for collagen production. L-arginine is a key component in and may mediate the beneficial effects of low protein diet. *(Narita I, et al, Proc Natl Acad Sci, 92, 4552, 1995)* The activation of macrophages by cytokines secreted by armed inflammatory CD4 T-cells is central to the host response to pathogens. Activated macrophages undergo changes that greatly increase their antimicrobial effectiveness and amplify immune responses, in particular by inducing the production of hydrogen peroxide and nitric oxide. These antimicrobial products can also damage host cells and so a series of enzymes, including catalase and superoxide dismutase (SOD) are produced during phagocytosis to control the action to act primarily on pathogens. *(Janeway C & Travers P, Immunobiology, Blackwell Scientific Publications, 1994)* SOD stabilises NO, whilst processes generating superoxide, conversely inactivate NO, itself having anti-oxidant function *(E Cadenas, Ch 1, in: Oxidative Stress and Antioxidant Defenses in Biology, S Ahmad (Ed), Chapman & Hall, 1995)*.

Just a decade ago, conventional wisdom held that mammals could not produce immunological reactive nitrogen intermediates (RNI) because they would be toxic. Recent studies into the role of reactive oxygen intermediates (ROI) and RNI in mammalian immunity show that in combination, the contribution of two enzymes, phagocyte oxidase (phox) and inducible nitric oxide synthase (NOS) to preventing microbial resistance to RNI, appears to be greater than previously appreciated, with each appearing to compensate in large part for isolated deficiency of the other. Animals deficient in the phox, the major source of pathogen-triggered ROI production, are susceptible to several inoculated pathogens. High output production of RNI is the specialty of mammalian phagocytes and is also attainable by many mammalian cells in response appropriate inflammatory stimuli. Even RNI of dietary origin are put to use as antimicrobial agents in gastric juice, a key component of the innate immune system of epithelium. Host defense epithelia with their antimicrobial armament, including T-cells and natural killer cells, are apparently incapable of ensuring the survival of the host against commensal organisms in the combined absence of phox and NOS, or medical intervention. *(Nathan C & Shiloh M, Proc Natl Acad Sci, USA, 97(16), 2000)* Nitric oxide plays a key role in neurotransmission, control of blood pressure and cellular defense mechanisms. Nitric oxide synthases catalyze the oxidation of L-arginine to NO. *(Boucher J, et al, Cell Molec Life Sci, 55(8/9), 1999)*

Active macrophages can produce superoxide in addition to NO. When L-arginine is limited, a high-output isoform of NOS can favor formation of a joint and particularly destructive cytotoxic product peroxynitrite *(Xia Y & Zweier J, Proc Natl Acad Sci, USA, 94: 6954, 1997)*, implicated in stroke, heart disease and immune complex-mediated pulmonary edema *(D Laskin & C Gardner, Ch 9, in: Toxicology of the Liver, G Plaa & W Hewitt (Eds), Taylor & Francis, 1998)*. The oxidative, inflammatory, mutagenic and cytotoxic potential of peroxynitrite contrasts with the antioxidant, anti-inflammatory and tissue-protective properties ascribed to NO itself *(Bryk R, et al, Nature, 14; 407, 2000)*. Phox and NOS 'inhibitors' are reportedly toxic in experimental animals, but L-arginine analogs (of which canavanine is one) in contrast, because of their similarity to arginine, are considered to be phox-sparing, nontoxic NOS inhibitors (with the obvious exclusion of canavanine). NOS is most readily observed in macrophages from patients with infectious or inflammatory diseases. Sustained production of NO endows macrophages with cytotoxic activity against viruses, bacteria, fungi, protozoa, helminths, and tumor *cells (MacMicking J, et al, Annu Rev Immunol, 15: 323, 1997); (Nathan C & Shiloh M, Proc Natl Acad Sci, USA, 97(16), 2000)* Immunocompetent cells rely on amino acids as energy substrates. Arginine in particular is a modulator of immunity and a greater availability improves the nonspecific immune response. *(Walrand S, et al, Am J Clin Nutr, 72(3), 2000)*

Nitric oxide is synthesised from L-arginine by NOS, of which there are two types, constitutive and inducible, and both of which are inhibited by L-arginine analogues. The NO released by the constitutive enzyme acts as a transduction mechanism underlying a large number of physiological responses. The inducible NOS is expressed after the activation of endothelial cells, macrophages and several other cells by cytokines. The only role for NO released by the inducible enzyme is as a cytotoxic molecule for invading micro-organisms and tumour cells. *(T Fan & M Dale, Ch 8 in: Textbook of Immunopharmacology, M Dale, et al (Eds), Blackwell Scientific Publications, 1994)* Dietary protein or arginine deficiency impairs constitutive and inducible NO synthesis *(Wu G, et al,* J Nutr *129: 1347, 1999)*. A recent review of the literature indicates that **NOS inhibitors (of which canavanine is one) have exacerbated infection by 80 species of viruses, bacteria, fungi, and protozoa** *(M DeGroote & F Fang, in: Nitric Oxide and Infection, F Fang (Ed), Kluwer/Plenum, pp. 231-264, 1999); (Nathan C & Shiloh M, Proc Natl Acad Sci, USA, 97(16), 2000)* Nitric oxide-mediated regulation of mitochondrial respiration represents a primary line of defense against oxidative and other stresses *(Paxinou E, et al, Proc Natl Acad Sci USA, 98(20), 2001)*, but aberrant production of NO contributes to the pathogenesis of diseases. Sustained NO production via NOS requires extracellular arginine uptake. *(Nicholson B, et al, J Biol Chem, 276(19), 2001)* **Sutherlandia is a NOS inhibitor.**

The production of NO represents an important component of the host immune response against viral infections, including retroviruses. Antiviral effects occur through its microbiostatic and microbicidal activity and probably also through its pro-inflammatory and immunoregulatory properties. AIDS is associated with activation of the immune system. Macrophages are suspected to play a major role in human immunodeficiency virus (HIV) infection. The impact of nitric oxide production on HIV-1 infection is still difficult to predict. HIV-1 stimulates NO production by human macrophages and NO concentration is increased in the sera of patients with AIDS, especially in those with neurological disorders and pulmonary disease caused by intracellular opportunistic pathogens. In vivo, human macrophages may synthesize detectable but very low production of NO during HIV infection, evidenced in AIDS patients, and in particular in individuals with opportunistic infections. The molecular mechanisms involved remain unclear, but the unusual low production of NO by HIV-infected human monocytes could explain the lack of antiviral activity against HIV. *(Blond D, et al, J Virol, 74(19), 2000)* Increased expression of NOS might be expected in HIV infections, yet elevated NO levels in serum are related only to active AIDS-related bacterial, protozoan, and fungal infections, rather than chronic viral infection with HIV alone. NO may play a role in the local control of chronic viral infections at tissue level, but this is not reflected in serum levels. *(Lake-Bakaar G, et al, Dig Dis Sci, 46(5), 2001)*

The high-output pathway of nitric oxide production helps protect mice from infection by several pathogens, including Mycobacterium tuberculosis. Macrophages in the lungs of people with clinically active Mycobacterium tuberculosis (Mtb) infection also express catalytically competent NOS. *(Nicholson S, et al, J Exp Med, 183(5), 1996)* Glucocorticoids regulate NO production following cytokine exposure primarily by limiting L-arginine availability *(Simmons W, et al, 271(39), 1996)*. Since the tuberculosis-exacerbating effect of corticosteroids is quantitatively indistinguishable from the effect of NOS deficiency, and corticosteroids suppress NOS, this may be an important mechanism for the tuberculosis-promoting effects of corticosteroids. *(Nathan C, J Clin Invest, 100(10), 1997)* Tuberculosis, the leading cause of death from infectious disease, poses an even greater threat as immunodeficiency spreads among the host population and drug resistance rises. NOS is necessary to control primary tuberculosis. In experimental mice, the absence of NOS leads to rapid bacterial growth, necrotic granulomatous pneumonitis, and death. In mice, as in people, the sterile eradication of Mtb is rarely achieved, suggesting that long-term $CD4^+$ memory T-cells must continually enlist the aid of macrophages to maintain bacterial dormancy. A requirement for NOS later during infection therefore could be expected if the host is to avoid disease recrudescence. Specifically inhibiting NOS during the late phase of clinical stability supports this hypothesis, because infection progresses more quickly and leads to earlier mortality. The fact that NOS is necessary to control mycobacterial growth, has implications for the global incidence of human tuberculosis, because Mtb currently infects over one-third of the world's population. *(MacMicking J, et al, Proc Natl Acad Sci, USA, 94(94; 5243; 1997)*

Any molecule whose expression is induced by signals associated with inflammation is likely to be detected in a wide variety of disease states. It is not surprising, then, that NOS has been detected in people at sites involved by Alzheimer's disease, multiple sclerosis, AIDS-associated dementia, asthma, lung cancer, pulmonary sarcoidosis, Crohn's disease, ulcerative colitis, rheumatoid arthritis, osteoarthritis, and psoriasis. The cytotoxic and pro-inflammatory potential of NOS advances the case for its therapeutic inhibition in those of the above diseases that are not thought to be infectious in etiology, or in those infectious diseases where the inflammatory effect of NOS appears to outweigh its antimicrobial effect. However, the anti-inflammatory role of NOS emphasizes the possibility of adverse consequences attendant on its inhibition. Expression of NOS sometimes makes a profound difference to the course of infection or inflammation. In both infection and inflammation, NOS appears to act both as a direct effector and as a regulator of other effectors. The impact of NOS is potentially dichotomous, and the dichotomy is sometimes manifest at different times or sites in the same experimental setting. These complexities do not preclude experimental therapeutic intervention, but demand caution when trials are with nitric oxide synthase inhibitors. *(Nathan C, J Clin Invest, 100(10), 1997)* Inhibitors of NOS (agents that prevent binding of substrate L-arginine) are potentially beneficial in the treatment of conditions associated with an overproduction of NO, including septic shock, neurodegenerative disorders, and inflammation. *(Hobbs A, et al, Annu Rev Pharmacol Toxicol, 39; 191, 1999)*

Conclusion. Canavanine-containing plants do have medicinal properties, but so do all plants, including common beverages, fruits, vegetables, nuts, seeds, culinary herbs and spices, often with far more documented beneficial properties and greater documented safety profiles. As a result, canavanine Sutherlandia products cannot be responsibly recommended over, or even in addition to and especially in the absence of good nutrition and it is clearly criminal to advocate otherwise. There is no scientific data to indicate that L-canavanine has any superiority over L-arginine as a health substance, indeed the very opposite is the case, so why not feed rather than poison?

1. My introduction to my Genocide and Ethnopiracy report is posted here: http://www.gaiaresearch.co.za/trads.html
2. My full Genocide and Ethnopiracy report is downloadable here: http://www.gaiaresearch.co.za/tramed.pdf
3. My recent letter to Mayeng is available here: http://www.gaiaresearch.co.za/pharmapact/Ethnopiracy.html
4. My original recent published paper is downloadable here: http://www.gaiaresearch.co.za/impila.pdf
5. My new PHARMAPACT health freedom website address is: http://www.gaiaresearch.co.za/pharmapact/

APPENDIX 1: Lupus overview (http://cerebel.com/lupus/overview.htm)

(H Michael Belmont, MD, Medical Director, Hospital for Joint Diseases, New York University Medical Center, 1998)

Systemic Lupus Erythematosus (SLE) is a chronic, usually life-long, potentially fatal autoimmune disease, characterized by unpredictable exacerbations and remissions with protean clinical manifestations. There is a predilection for clinical involvement of the joints, skin, kidney, brain, serosa, lug, heart and gastrointestinal tract.

SLE is an autoimmune disease characterized by immune dysregulation, resulting in the production of antinuclear antibodies, generation of circulating immune complexes, and activation of the complement system. SLE is notable for unpredictable exacerbations and remissions and a predilection for clinical involvement of the joints, skin, kidney, brain, serosa, lung, heart, and gastrointestinal tract. The pathologic hallmark of the disease is recurrent, widespread, and diverse vascular lesions. The clinical features of SLE are protean and may mimic infectious mononucleosis, lymphoma, or other systemic disease. The etiology remains unknown. A genetic predisposition, sex hormones, and environmental trigger(s) likely result in the disordered immune response that typifies SLE.

The origin of auto-antibody production in SLE is unclear but a role is suggested for an antigen driven process, spontaneous B-cell hyper-responsiveness, or impaired immune regulation. Regardless of the etiology, SLE is associated with the impaired clearance of circulating immune complexes secondary to decreased CR1 expression, defective Fc receptor function, or deficiencies of early complement components such as C4A. More is known about the pathogenic cellular and molecular events responsible for vascular lesions than the origins of autoimmunity.

Disease manifestations result from recurrent vascular injury due to immune complex deposition, leukothrombosis, or thrombosis. Additionally, cytotoxic antibodies can mediate autoimmune hemolytic anemia and thrombocytopenia, while antibodies to specific cellular antigens can disrupt cellular function. The health status of a patient is related not only to disease activity, but to the damage that results from recurrent episodes of disease flare (deforming arthropathy, shrinking lung, end stage renal disease, organic mental syndrome, etc.), as well as the adverse effects of treatment (i.e. avascular necrosis of bone, infections, and precocious atherosclerosis, etc.).

Drugs such as procainamide or hydralazine can induce the production of antinuclear antibodies, especially anti-histone antibodies, and occasionally a SLE-like illness. Drug induced lupus is usually characterized by fever, hematological abnormalities such as an autoimmune hemolytic anemia or autoimmune thrombocytopenia, or serositis. Skin, renal and neurologic manifestations are uncommon. Neonatal or congenital lupus occurs when the transplacental acquisition of auto-antibodies produce in the neonate a transient photosensitive rash, confential complete heart block, thrombocytopenia or rarely hepatobiliary dysfunction.

Presenting Signs and Symptoms: 80% of patients with SLE will present with involvement of the skin or joints. A common presenting complaint is a photosensitive rash often with alopecia. Alternatively, patients may present with arthralgia or frank arthritis. However, patients may present with fever accompanied by single organ involvement, such as inflammatory serositis, glomerulonephritis, neuropsychiatric disturbance or hematological disorder (autoimmune hemolytic anemia or thrombocytopenia).

Constitutional: 90% of patients with SLE experience fatigue. Arthralgia and myalgia often accompany complaints of malaise. Also common and a more serious constitutional feature of SLE is persistent fever and weight loss.
Musculoskeletal: Approximately 90% of patients with SLE have musculoskeletal symptoms, typically arthralgia. Less common is frank inflammatory myositis, which occurs occasionally during the course of SLE.
***Mucocutaneous*:** Mucosal ulcers are not an infrequent complication of lupus, occurring in 30% of patients, painful when there is a secondary infection, such as oral candidiasis.
Dermacutaneous*:* *Approximately 80% of patients with SLE have dermatological manifestations during the course of their illness, manifest as a photosensitive rash. Alopecia occurs in 50% of patients, typically manifest as reversible hair thinning during periods of disease activity.*
Hematological: Anemia is a common feature of exacerbated SLE. Autoimmune thrombocytopenia purpura can be a presenting feature, as can thrombocytopenia and leukopenia with lymphopenia.
Renal: Although the majority of patients with SLE have glomeruplopathy, clinically relevant kidney disease occurs in about 50% of patients, a consequence of deposition of immune complexes containing anti-DNA in the kidney.
Central Nervous System: Neuropsychiatric complications occur in 50% of SLE patients and include acute and chronic, as well as focal and diffuse manifestations. Seizures complicate the course in 25% of patients. Recurrent involvement of the central nervous system may result in an organic brain syndrome and dementia.
Lung: The most common involvement of the lung is inflammatory serositis, producing pleuritis. However, patients with lupus can develop transient hypoxia on the basis of pulmonary leukosequestration, inflammatory pneumonitis, interstitial pulmonary fibrosis, pulmonary hypertension, diaphragmatic dysfunction, and phrenic nerve palsy.
Cardiac: The most common cardiac manifestation is pericarditis and myocarditis.
Gastrointestinal: Medical peritonitis with or without ascites is a manifestation of lupus involving the peritoneum.