Current and future prospects of integrating traditional and alternative medicine in the management of diseases in Tanzania

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Abstract: Traditional medicine and medicinal plants, in general, continue to be a powerful source of new drugs, now contributing about 90% of the newly discovered pharmaceuticals. Traditional medicine continues to provide health coverage for over 80% of the world population, especially in the developing world. The past and the present are all full of living examples of discoveries of drugs, ranging from anticancer, antiasthma, antidiabetic, antihypertensives and many others which owe their origin to traditional medicine. The current era of HIV/AIDS is not short of contributions from traditional medicine. The recent discovery of the non-nucleoside reverse transcriptase inhibitor (NNRTI), calanolide A, is a new addition from traditional medicine. Many more such discoveries are yet to come. While this potential is much acknowledged, little has been done in African countries, to utilize the plants that are already known and proven to be safe for use by patients. A number of plants could be widely cultivated for local industrial production of medicines and herbal nutritional supplements. There is need to ensure that what is known is made use of, for financial gain, and for improvement of the health of our people. We need to establish the necessary expertise for development of traditional medicines and deliberate efforts should be made to encourage local industrial production of traditional/herbal medicines so that cultivation may become possible and hence contribute to poverty reduction.

Keywords: Traditional medicine, alternative medicine, diseases, Tanzania

Introduction

The world is currently facing a number of health challenges, partly due to expanded boundaries of diseases as a result of global warming, improved means of transportation and increased migration of people. It is also acknowledged that the change of lifestyle in the developing world, where people are now leading sedentary lives, and have greatly changed types of food essentially consuming more refined foods has now led to increase in the prevalence of glucose intolerance (King & Rewers, 1993). Likewise there have emerged new diseases such as HIV/AIDS, Ebola, and human spongiform encephalopathy (Budka *et al.,* 1995; Van Everbroeck *et al.,* 2000; Brown *et al.,* 2004) that do not yet have a cure. Re-emergence of diseases like tuberculosis and the emergence of pathogens that are resistant to the currently available chemotherapeutic agents, is yet another challenge of our times. The living example is the emergence of multi-drug resistant (MDR) *Mycobacterium tuberculosis*. Malignant tumors and some important parasites, like *Plasmodium falciparum* and *Candida albicans* are also developing resistance, thus making management of diseases more and more difficult. Amidst this crisis, the synthetic chemist is long recognized to have failed to address these health challenges. The only rational alternative is therefore, traditional medicine, which according to WHO supports more than 80% of the population in developing countries, and it is now widely accepted that traditional medicines are more affordable, less toxic, and have a wide acceptance around the world (Cowan, 1999; WHO, 2002).

Nature has been a source of medicinal treatments for thousands of years, and plant-based systems continue to play an essential role in the primary health care. It is estimated that 25 to 50% of all current pharmaceuticals are derived from plants (Cowan, 1999). In fact, it is now believed that plant based systems contribute 90% of the newly discovered pharmaceuticals. Nature has provided many of the effective anticancer agents in current use, such as the microbially derived drugs, dactinomycin, bleomycin, and doxorubicin, and the plant-derived drugs vinblastine, irinotecan, topotecan, etoposide, and paclitaxel (Cragg *et al.,* 1997). Traditional medicine, has particularly, been a good source of these plant derived drugs. This paper examines some evidences and indicators of

prospects for the use of traditional medicines in the management of different diseases, and some efforts in the discovery of drugs for the management of HIV/AIDS and associated opportunistic conditions. Literature reports and some results generated from our own research have been used to build up a case for the possibility that traditional medicine could be a source of drugs for the management of patients in Tanzania.

Terminalia sericea (Moshi & Mbwambo, 2005) and *Terminalia mollis* (M. Moshi & Z. Mbwambo, *unpublished*), which are used in traditional medicine in Tanzania have potential to yield anticancer compounds. Work done using brine shrimps as a screening tool shows that extracts of the two plants have activity which compares very favorably with the standard drug cyclophosphamide (Table 1). Ongoing studies on the combretastatins, and other

Table 1: The brine shrimp lethality test of *Terminalia sericea* root extracts. The results are reported as LC_{50} values with the 95% confidence intervals (CI).

Extract type	LC_{50}	95% CI
Petether extract	121.0	108.0–135.5
Dichloromethane extract	29.9	21.2– 42.2
Ethylacetate	16.4	11.8–22.6
Dichloroethane:methanol (1:1)	5.4	4.1–7.2
Methanol extract	16.9	15.2–18.8
80% Ethanol extract	17.4	11.4–26.5
Aqueous extract	5.4	3.5–8.4
Butanol extract	5.8	4.1–8.1
Cyclophosphamide	16.3	10.6-25.2

Traditional medicine in the discovery of anticancer drugs

One good example is the plant *Catharanthus rosea* which was used in Madagascar for treatment of diabetes. Through use, it was later observed that extracts of the plant suppress the bone marrow. Follow up of this observation led to the discovery and the isolation of the anticancer compounds vincristine, vinblastine, and vinorelbine. The compound taxol which was first isolated from the Pacific yew, *Taxus brevifolia*, was found to have anticancer activity. This has now resulted in the synthesis of the analogues paclitaxcel and docetaxel, which now constitute a new class of broad spectrum anticancer compounds.

Plants of the family Combretaceae are widely used in traditional medicine in South Africa (Eloff, 1999) and Tanzania (Fyhrquist *et al.,* 2004; Moshi & Mbwambo, 2005). The plants of this family are now a source of combretastatins, a new class of antimitotic drugs that also inhibit angiogenesis and are currently being developed for the treatment of cancer. Work done in our laboratory has shown that compounds, from this family hold a promise for new anticancer drugs.

Traditional medicine in the discovery of antimalarial drugs

Cinchona bark was used for the treatment of malaria by South American Indians. This led to the isolation of quinine in the seventeenth century. Based on the structure of quinine other analogues have been synthesized. Mefloquine is a quinoline methanol with a structure similar to that of quinine. Other antimalarials which were synthesized based on the structure of quinine include the 4-aminoquinolines (chloroquine and amodiaquine), 8-aminoquinolines (primaquine and tefenaquine), and the aryl alcohols (halofantrine, lumefantrine, and pyronaridine). Recently, from the Chinese traditional medicine, quinghasou, the antimalarials artemisinin, dihydroartemisinin, artemether, and arteether have been discovered (Meshnick *et al.,* 1996). A number of other plants from traditional medicine have shown antimalarial activity and have potential for discovery of future antimalarials.

Traditional medicine in the discovery of anti-asthma drugs

Khellin from *Amni visnaga* was used in the USA as a bronchodilator. It was then discovered that after prolonged use it produces nausea and vomiting. As an attempt to synthesize khellin analogues with fewer side effects the antiasthma drug chromolyn (Sodium chrogycate was discovered (Sneader, 1985). Sodium chromogylycate is now used to stabilize the membranes of macrophages and prevent degranulation, and hence release of mediators of broncho-constriction in asthmatic patients.

Traditional medicine in the discovery of antidiabetic drugs

Galega officinalis (L.) was used ethnomedically for the treatment of diabetes. Phytochemical work led to the isolation of the antihyperglycaemic compound galegine from the plant. Further structure activity studies and modification of galegine led to the synthesis of metformin and eventually the other biguanide oral hypoglycaemic agents (Sneader, 1985). Harunganin was recently isolated from a Tanzanian plant, *Harungana madagascariensis* and is now patented in the USA for treatment of diabetes (Inman & Luo, 1998).

Other compounds recently isolated from traditionally used plants and patented for treatment of diabetes include cryptolepine (Bierer *et al.,* 1998a,b; Luo *et al.,* 1998), maprouneacin (Carne*y et al.,* 1999), 3ß,30-dihydroxylupen-20(29)-en-2-one (Inman & Reed, 1997,1998), vismin (Inman & Luo, 1998), and quinones SP18904 and SP18905 (Luo *et al.,* 1999). The most interesting discovery was nordihydroguaiaretic acid (ndga) (Luo *et al.,* 1998) which, besides being active orally in diabetic mice, also lowered cholesterol levels.

Traditional medicine in the discovery of anti-HIV drugs

The use of traditional medicines for the management of HIV/AIDS patients is directed to three main areas; direct effect on the virus, immunostimulant activity, and treatment of opportunistic infections. A number of plants have now been identified from random screening or from traditional systems of treatment that interfere with nearly all stages of the viral life cycle. Compounds have been reported that inhibit virus-cell fusion, reverse transcription, virus adsorption, and proteolytic cleavage (Vlietinck *et al.,* 1998; Wang *et al.,* 1998; Uchiumi *et al.,* 2003). A good number of plants containing these compounds, such as *Phyllanthus amarus* (Notka *et al.,* 2004), *Phyllanthus niruri* (Naik & Juvekar, 2003), *Salvia miltiorrhiza* (Abd-Elazem *et al.,* 2002), *Shepherdia argentea* (Yoshida *et al.,* 1996), *Viola yedoensis, Arctium lappa, Epimedium grandiflorum, Glycyrrhiza uralensi*s and *Castanospermum australe* (WHO, 1989), and *Croton tiglium* (Nakamura, 2004) originate from traditional medicine. Other traditionally used medicines that have shown anti-HIV activity are *Aspilia pluriseta* and *Rumex bequaertii* (Cos *et al.,* 2002). In a recent study done on 21 plant species belonging to 14 families of plants, that are used in Ethiopian traditional medicine, extracts of four plants, *Bersama abyssinica* Fresen, *Combretum paniculatum* Vent., *Dodonaea angustifolia* L.f., and *Ximenia americana* L. displayed anti-HIV activity against both HIV-1 and HIV-2 strains (Asres *et al.,* 2001). Similarly screening of plants used in traditional medicines of other countries has led to identification of interesting anti-HIV activity (Abdel-Malek *et al.,* 1996; Piras *et al.,* 1997; Li *et al.,* 1993).

The most recent success story is the discovery of (+)-Calanolide A, a novel non-nucleoside HIV-1-reverse transcriptase inhibitor (NNRTI), which was first isolated from a Malaysian plant, *Calophyllum lanigerum* (Currens *et al.,* 1996; Buckheit *et al.,* 1999; Creagh *et al.,* 2001). The anti-HIV properties of Calanolide A show that it is effective towards multiple NNRTI-resistant mutations that include the highly resistant Y181C mutation. Clinical viral isolates that are resistant to nucleoside analogues have been shown to be hypersensitive to the anti-viral effects of Calanolide A. In laboratory experiments Calanolide A also works synergistically towards HIV when used with other anti-HIV drugs. The drug is being developed by Sarawak MediChem and is now undergoing phase III clinical trials. A recently published article reported results showing that Calanolide A is also active against both drug-sensitive and drug-resistant *Mycobacterium tuberculosis* (Xu *et al.,* 2004).

Sutherlandia frutescens and *Lobostemon trigonu* are two plants that are marketed in South Africa for the treatment of HIV/AIDS patients. A recent study has, now provided proof, that the two plants have inhibitory activity against HIV-1 reverse transcriptase activity (Harnett *et al.,* 2005). Clinicians treating HIV+ patients with Sutherlandia tablets produced by the South African company Phyto Nova have reported increase in CD4 and reduction of viral load. Sutherlandia is also reported to have apoptotic activity against human cancer cell lines (Chinkwo, 2005), thus suggesting an additional potential for dealing with opportunistic malignancies in HIV patients.

Aloe vera has also being very popular in South Africa. The plant contains a large variety of amino acids, enzymes, vitamins and minerals and it comes closer than any other known plant to the duplication of life's essential substances in the biochemistry of the human body. It has natural healing and detoxifying powers and works gently within the intestinal tract to help break down impacted food residues and thoroughly cleanse the bowel. It can help ease constipation and prevent continuing diarrhoea, setting a regularity to the bowel. All this helps to reduce discomfort and bloating. Naturally, as these symptoms are eased, so the stress associated with the discomfort is also reduced. *Aloe vera* is a stimulant to the immune system, a powerful anti-inflammatory, and analgesic and is able to speed up cell growth. *Aloe vera* contains a large number of mucopolysaccharides (basic sugars) which are found in every cell in the body and contains large numbers of nutrients including vitamins E, C, B1, 2, 3, and 6 as well as iron, manganese, calcium and zinc. Seven essential amino acids and fatty acids are also found in *Aloe vera* (Davis & Leitner, 1989; Davis & Rosenthal, 1989; Pulse & Uhlig, 1990; Sato, 1990; McCluggage & Higdon, 1999). This plant should be promoted as a nutritional supplement to HIV/AIDS patients, who are likely to realize a lot of benefit from its use. The big question is whether such use may not have interactions, particularly with concurrent use with anti-retroviral drugs. However, this should be one of the areas that need intensive scientific studies.

Traditional medicines in the treatment of bacterial infections

The other area where traditional medicines can offer hope is in the treatment of opportunistic infections. Our experience shows that there are a number of plants with a good potential for offering solutions to resolution of bacterial, fungal, viral, protozoa, and other opportunistic infections. There are now abundant reports of useful activities of plants of the genera Combretum and Terminalia. A number of species of Combretum and Terminalia from South Africa have antibacterial activity (Eloff, 1999). The plants in the two genera are heavily used in traditional medicine in South Africa with an annual consumption of 20.2 tons per year in Kwazulu Natal (Eloff, 1998). In Tanzania the plants in the two genera are also popularly used in traditional medicine for the treatment of bacterial infections (Fyhquist *et al.,* 2004, 2005; Moshi & Mbwambo, 2005). *Combretum micranthum* which is used traditionally in West Africa for treatment of biliary fever, colic and vomiting, showed good antibacterial activity against both gram positive and gram negative bacteria.

In a recent study we looked at the antibacterial properties of *Terminalia sericea* (Moshi & Mbwambo, 2005) and *Terminalia mollis* (unpublished results), in which we showed that these two plants growing in Tanzania have antimicrobial activity, thus confirming reports from traditional healers in Iringa, Tabora and Bukoba where they were collected. The two plants are used for treatment of bacterial infections such as gonorrhoea and tuberculosis, and also dysentery, diarrhoea and malaria.

Traditional medicines for treatment of fungal infections

A number of plants used in traditional medicines are currently being identified for the treatment of opportunistic fungal infections in HIV patients (Fyhrquist *et al.,* 2004; Motsei *et al.,* 2003). Some of the already identified plants could be used as oral mouth preparations (Motsei *et al.,* 2003), and others could be made in the form of ointments or creams for use on the skin. Studies done on some

Combretaceae plants indicate the possibility of getting clinically useful antifungal activity, particularly against *Candida albicans* and other yeast-like fungi (Moshi & Mbwambo, 2005). In a recent ethnomedical survey, in Morogoro rural (Mikese), Singida, Lushoto, and Coast region (Chalinze, Bagamoyo, Chamakwesa, and Mabwepande) in Tanzania, 58 plants used for treatment of fungal infections were identified. Out of these plants 10 gave very good antifungal activity in the laboratory. Other plants collected in Bukoba, Tanzania have also indicated possibility that they may be good for treatment of fungal infections. These plants and others are currently being screened for toxicity using the brine shrimps test in our laboratory. The preliminary results show that a good number of the plants for treatment of fungal infections have a good safety margin (Table 2). Some of these plants are being tested for the treatment of topical fungal infections, and already there are good responses among patients using them.

Table 2: Brine shrimp lethality of aqueous ethanolic extracts of plants used traditionally for treatment of fungal infections

Binomial name	Vernacular name	Part tested	LC_{50} µg/ml (95% CI)*
Acacia nilotica	Mkame	Leaves	108.5 (87.8-134.0)
Acalypha fruticosa	Siaiti	Roots	23.9 (16.5-34.7)
Acalypha fruticosa	Siaiti	Leaves	113.9 (91.2-142.3)
Aloe lateritia	Mapuni, Nyamviri	Leaves	19.1 (13.2-27.8)
Cordia Africana	Mngwengweni	Roots	211.4 (117.6-380.1)
Cyphosterma hilderbrandtii	Damanya mwili		25.7 (16.9-39.0)
Elaeodendron schlechteranum	Mkandekande	Stem bark	37.5 (28.1-50.1)
Euphorbia heterophylla	Loo	Leaves	80.2 (57.3-112.3)
Ficus sur	Mkuyu	Bark	146.1 (116.1-183.9)
Hypericum roeperanum	Mwambaziwa	Leaves	46.6 (34.2-63.6)
Jatropha multifida	Maugamwipoli	Leaves	21.7 (16.4-28.7)
Jatropha multifida	Maugamwipoli	Stem	58.3 (41.3-82.4)
Jatropha multifida	Maugamwipoli	Roots	26.1 (17.3-39.2)
Khaya anthotheca	Mgolaminzi	Stem bark	38.7 (28.6-52.2)
Kigelia africana	Mungungu	Roots	7.2 (3.9-13.8)
Kigelia africana	Mungungu	Fruits	4.6 (3.2-6.6)
Lannea stuhlmannii	Muhungilo	Leaves	25.3 (16.6-38.8)
Ocimum suave	Suameno	Leaves	16.7 (11.6-24.1)
Rapanea melanophloeus	Mpaja	Stem bark	152.4 (84.6-274.5)
Rapanea melanophloeus	Mpaja	Leaves	12.1(8.6-17.2)
Spirostachys africana	Muhoza	Leaves	16.4 (9.4-28.8)
Tegetes minuta	Mbangi		19.9 (14.5-27.3)
Zehneria seabra	Fuia	Leaves	138.1(93.7-203.4)
Ziziphus pubercens	Inyigrishi	Leaves	68.2 (50.5-92.1)
Cyclophosphamide	Standard drug		16.3 (10.6-25.2)

*The results are reported as LC_{50} values with the 95% confidence intervals

Efforts to use already established plants

Prospects for incorporating traditional medicines into the health care system are quite high, if appropriate measures are taken to ascertain the claimed activities, and obvious toxicities that may prevent immediate use. In many instances traditional healers use these plants in a manner that avoids the toxic manifestations. Biological testing coupled with a quick evaluation for toxicity should allow an accelerated use of traditional medicines without a lot of fear about toxicity, especially where such medicines are going to be used for a short period, such as in the treatment of bacterial, fungal and protozoan infections. For example, *Terminalia sericea* gave positive antibacterial activity against gram positive and gram negative bacteria and antifungal activity against *C. albicans,* but it also showed toxicity on brine shrimps, suggesting either outright toxicity or presence of anticancer activity, since the results compared very well with the values obtained with the standard anticancer drug cyclophosphamide (Moshi & Mbwambo, 2005). It is known that Combretaceae plants contain combretastatins, which have anticancer activity.

Our Institute is now piloting the production of herbal formulations of already proven plants. Currently herbal preparations for benign prostatic hypertrophy, peptic ulcers, coughing, livers cirrhosis and asthma are being produced at the Institute. Efforts are underway to standardize these formulations and make them available to many more people in Tanzania. The production is going hand in hand with promotion of cultivation of some of the medicinal plants such as *Adansonia digitata, Moringa oleifera, Hibiscus subdariffa* variety Rosera, and *Aloe vera*. It is expected to involve the community in the cultivation of these medicinal plants.

Conclusion

Traditional medicines are now the mainstay of drug discovery, for treatment of old and emerging diseases. The options of using them as herbal medicines or for isolation of patentable compounds remain attractive to researchers in Tanzania and elsewhere. However, there is need to ensure that what is known is made use of, for financial gain, and for improvement of the health of our people. We need to establish the necessary expertise for development of traditional medicines and deliberate efforts should be made to encourage local industrial production of traditional/herbal medicines so that cultivation may become possible and hence contribute to poverty reduction.

References

Abdel-Malek, S., Bastien, J.W., Mahler, W.F., Jia, Q., Reinecke, M.G., Robinson, W.E. Jr, Shu, Y. & Zalles-Asin, J. (1996) Drug leads from the Kallawaya herbalists of Bolivia.1. Background, rationale, protocol and anti-HIV activity. *Journal of Ethnopharmacology* **50,** 157-166.

Abd-Elazem, I.S., Chen, H.S., Bates, R.B. & Huang, R.C. (2002) Isolation of two highly potent and non-toxic inhibitors of human immunodeficiency virus type 1 (HIV-1) integrase from *Salvia miltiorrhiza. Antiviral Research* **55**, 91-106.

Asres, K., Bucar, F., Kartinig, T., Witvrouw, M., Pannecoupue, C. & De Clercq, E. (2001) Antiviral activity against human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) of ethnobotanically selected Ethiopian medicinal plants. *Phytotherapy Research* **15,** 62-69.

Bierer, D.E., Fort, D.M., Mendez, C.D., Luo, J., Imbach, P.A., Dubenko, L.G., Jolad, S.D., Gerber, R.E., Litvak, J., Lu, Q., Zhang, P., Reed, M.J., Waldeck, N., Bruening, R.C., Naomesi, B.K., Hector, R.F., Carlson, T.J. & King, S.R.(1998a) Ethnobotanical-directed discovery of the antihyperglycemic properties of cryptolepine: its isolation from *Cryptolepis sanguinolenta*, synthesis, and *in vitro* and *in vivo* activities. *Journal of Medicinal Chemistry* **41**, 894-901.

Bierer, D.E., Dubenko, L.G. Zhang, P., Lu, Q., Imbach, P.A., Garofalo, A.W., Phuan, P., Fort, D.M., Litvak, J., Gerber, R.E., Sloan, B., Luo, J., Cooper, R. & Reaven, G.M. (1998b) Antihyperglycemic activities of cryptolepine analogues: an ethnobotanical lead structure isolated from *Cryptolepis sanguinolenta*. *Journal of Medicinal Chemistry* **41**, 2754-2764.

Brown, P., Gibbs Jr., C.J., Rodgers-Johnson, P., Asher, D.M., Sulima, M.P., Bacote, A. & Gajdusek, D.C. (2004) Human spongiform encephalopathy: The National Institute of Health series of 300 cases of experimentally transmitted disease. *Annals of Neurology* **35**, 513-529.

Buckheit, R.W., Jr., White, E.L., Fliakas-Boltz, V., Russell, J., Stup, T.L., Kinjerski, T.L., Osterling, M.C., Weigand, A. & Bader, J.P. (1999) Unique anti-human immunodeficiency virus activity of the nonnucleoside reverse transcriptase inhibitors calanolide A, costatolide and dihydrocostatolide. *Antimicrobial Agents and Chemotherapy* **43**,1827-1834.

Budka, H., Aguzzi, A., Brown, P., Brucher, J.M, Bugiani, O., Collinge, J., Diringer, H., Gullotta, F., Haltia, M. & Hauw, J.J. (1995) Neuropathological diagnostic criteria for Creutzfeldt-Jakob disease (CJD) and other human spongiform encephalopathies (prion diseases). *Brain Pathology* **5**, 319-322.

Carney, J.R., Krenisky, J.M., Williamson, R.T., Luo, J., Carlson, T.J., Hsu, V.L. & Moswa, J.L. (1999) Maprouneacin, a new daphnane diterpenoid with potent antihyperglycemic activity from *Maprounea africana*. *Journal of Natural Products* **62**, 345-347 .

CDC (1990) Guidelines for national human immunodeficiency virus case surveillance, including monitoring for human immunodeficiency virus infection and acquired immunodeficiency syndrome. *MMWR Morbidity and Mortality Weekly Reports* **48** (RR-13), 1-27, 29-31.

Chinkwo, K.A. (2005) *Sutherlandia frutescens* extracts can induce apoptosis in cultured carcinioma cells. *Journal of Ethnopharmacology* **98,** 163-170.

Cos, P., Hermans, N., De, B.T., Apers, S., Sindambiwe, J.B., Witvrouw, M., De, C.E, Vanden, B.D., Pieters, L. & Vlietinck, A.J. (2002) Antiviral activity of Rwandan medicinal plants against human immunodeficiency virus type-1 (HIV-1). *Phytomedicine* **9**, 62-68.

Cowan, M.M. (1999) Plant products as antimicrobial agents. *Clinical Microbiology Reviews* **12**, 564-582.

Cragg, G.M., Newman, D.J. & Weiss, R.B. (1997) Coral reefs, forests, and thermal vents: the worldwide exploration of nature for novel antitumor agents. *Seminars in Oncology* **24**,156-163.

Creagh, T., Ruckle, J.L., Tolbert, D.T., Giltner, J., Eiznhamer, D.A., Dutta, B., Flavin, M.T. & Xu, Z. (2001) Safety and pharmacokinetics of single doses of (+)-calanolide A, a novel, naturally occurring nonnucleoside reverse transcriptase inhibitor, in healthy, human immunodeficiency virus negative-negative human subjects. *Antimicrobial Agents and Chemotherapy* **45**, 1379-1386.

Currens, M.J., Gulakowski, R.J., Mariner, J.M., Moran, R.A., Buckheit, R.W. Jr., Gustafson, K.R., McMahon, J.B. & Boyd, M.R. (1996) Antiviral activity and mechanism of action of calanolide A against the human immunodeficiency virus type-1. *Journal of Pharmacology and Experimental Therapeutics* **279**, 645-651.

Davis, R.H. & Leitner, M.G. (1989) Wound healing, oral and topical activity of *Aloe vera*. *Journal of American Podiatric Medical Association* **79**, 559-562.

Davis, R.H. & Rosenthal, K.Y., (1989) Processed *Aloe vera* administered topically inhibits inflammation. *Journal of American Podiatric Medical Association* **79,** 395-397.

Eloff, J.N. (1999) The antibacterial activity of 27 Southern African members of the Combretaceae. *South African Journal of Science* **95**, 148-152.

Fyhrquist, P., Mwasumbi, L., Haeggstrom, C.A., Vuorela, H., Hiltunen, R. & Vuorela, P., (2004) Antifungal activity of selected species of Terminalia, Pteleopsis and Combretum (Combretaceae) in Tanzania. *Pharmaceutical Biology* **42**, 308-317.

Harnett, S.M., Oosthuizen, V. & Van de Venter, M. (2005) Anti-HIV activities of organic and aqueous extracts of *Sutherlandia frutescens* and *Lobostemon trigonus*. *Journal of Ethnopharmacology* **96**, 113-119.

Inman, W.D. & Reed, M.J. (1997) Triterpenoid compound for the treatment of diabetes. In: *U.S. Patent.* South San Francisco, CA: Shaman Pharmaceuticals.

Inman, W.D. & Luo, J. (1998) Hypoglycemic agents from *Harungan* or *Vismia* spp. WO 98 25,639. In: *U.S. Patent*. South San Francisco, CA: Shaman Pharmaceuticals.

King, H., & Rewers, M. (1993) Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. WHO Ad Hoc Diabetes Reporting Group. *Diabetes Care* **16**, 157-177.

Li, B.Q., Fu, T., Yan, Y.D., Baylor, N.W., Ruscetti, F.W. & Kung, H.F. (1993) Inhibition of HIV infection by baicalin - a flavonoid compound purified from Chinese herbal medicine**.** *Cellular and Molecular Biology Research* **39,** 119-124.

Luo, J., Chuang, T., Cheung, J., Quan, J., Tsai, J., Sullivan, C., Hector, R.F., Reed, M.J., Meszaros, K., King, S.R., Carlson, T.J. & Reaven, G.M. (1998) Masoprocol (nordihydroguaiaretic acid): a new antihyperglycemic agent isolated from the creosote bush (*Larrea tridentata*). *European Journal of Pharmacology* **346**, 77-79.

Luo, J., Cheung, J., Yevich, E.M., Clark, J.P., Tsai, J., Lapresca, P., Ubillas, R.P., Fort, D.M., Carlson, T.J., Hector, R.F., King S.R. Mendez, C.D., Jolad, S.D. & Reaven, G.M. (1999) Novel terpenoid-type quinones isolated from *Pycnanthus angolensis* of potential utility in the treatment of type 2 diabetes. *Journal of Pharmacology and Experimental Therapeutics* **288**, 529-534.

McCluggage, D. & Higdon, P.L. (1999) *Holistic Care for Birds: A Manual of Wellness and Healing*. Wiley Publishers.

Meshnick, S.R., Taylor, T.E. & Kamwonwongpaisan, S. (1996) Artemisinin and the antimalarial endoperoxides: from herbal remedy to targeted chemotherapy. *Microbiology Reviews* **60**, 301-315.

Moshi, M.J. & Mbwambo, Z.H. (2005) Some pharmacological properties of extracts of *Terminalia sericea* roots. *Journal of Ethnopharmacology* **97,** 43-47.

Motsei, M.L., Lindsey, K.L., van Staden, J. & Jager, A.K. (2003) Screening of traditionally used South African plants for antifungal activity against *Candida albicans*. *Journal of Ethnopharmacology* **95**, 235-241.

Naik, A.D. & Juvekar, A.R. (2003) Effects of alkaloidal extract of *Phyllanthus niruri* on HIV replication. *Indian Journal of Medical Sciences* **57**, 387-393.

Notka, F., Meier, G. & Wagner, R. (2004) Concerted inhibitory activities of *Phyllanthus amarus* on HIV replication *in vitro* and *ex vivo*. *Antiviral Research* **64**, 93-102..

Piras, G., Makino, M. & Baba, M. (1997) Sho-saiko-to, a traditional Kampo medicine, enhances the anti-HIV-1 activity of lamivudine (3TC) *in vitro. Microbiology and Immunology* **41**, 835-839.

Pulse, T.L. & Uhlig, E. (1990) A significant improvement in a clinical pilot study utilizing nutritional supplements, essential fatty acids and stabilized *Aloe vera* juice in 29 HIV seropositive, ARC and AIDS patients. *Journal of Advancement in Medicine* **3**, 4.

Sato, Y. (1990) Protection effects of *Aloe arborescens* on skin injury by X-irradiation. *Yakmgakn Zasshi* **110,** 876-884.

Sneader, W. (1985) *Drug Discovery: The Evolution of Modern Medicines*. New York:Wiley.

Sun, I.C., Chen, C.H., Kashiwada, Y., Wu, J.H., Wang, H.K. & Lee, K.H. (2002) Anti-AIDS AGENTS 49. synthesis, anti-HIV, and anti-fusion activities of IC9564 analogues based on betulinic acid. *Journal of Medicinal Chemistry* **12**, 4271-4275.

Uchiumi, F., Hatano, T., Itoh, H., Yoshida, T. & Tanuma, S. (2003) Transcriptional suppression of the HIV promoter by natural compounds. *Antiviral Research* **58**, 89-98.

Van Everbroeck, B., Pals, P., Dziedzie, T., Dom, R., Godfraind, C., Sciot, R., Brucher, J.M., Martin, J.J. & Cras, P. (2000) Retrospective study of Creutzfeldt-Jakob disease in Belgium: neurophysiological findings. *Acta Neoropathologica* (Berl) **99**, 358-364.

Vlietinck, A.J., De Bruyne, T., Apers, S. & Pieters, L.A. (1998) Plant-derived leading

compounds for chemotherapy of human immunodeficiency virus (HIV) infection. *Planta Medica* **64**, 97-109.

Wang, H.K., Xia, Y., Yang, Z.Y., Natschke, S.L. & Lee, K.H. (1998) Recent advances in the discovery and development of flavonoids and their analogues as antitumor and anti-HIV agents. *Advances in Experimental Medicine and Biology* **439**, 191-225.

WHO (1989) *In vitro* screening of traditional medicines for anti-HIV activity: memorandum from a WHO meeting. *Bulletin of the World Health Organization* **67**, 613-618.

WHO (2002) *Traditional Medicine: Growing Needs and Potential*. *WHO Policy Perspectives on Medicines*. World Health Organization, Geneva pp. 1-6.

Xu, Z.Q., Barrow, W.W., Sulling, W.J., Westbrook, L., Barrow, E., Lin, Y.M. & Flavin, M.T. (2004) Anti-HIV natural product (+)-calanolide A is active against both drug-susceptible and drug-resistant strains of *Mycobacterium tuberculosis*. *Bioorganic Medicinal Chemistry* **12**, 1199-1207.

Yoshida, T., Itoh, H., Hatano, T., Kurata, M., Nakanishi, T., Inada, A., Murata, H., Inatomi, Y., Matsuura, N., Ono, K., Nakane, H., Noda, M., Lang, F.A. & Murata, J. (1996) New hydrolyzable tannins, shephagenins A and B, from *Shepherdia argentea* as HIV-1 reverse transcriptase inhibitors. *Chemical and Pharmaceutical Bulletin* (Tokyo) **44**, 1436-1439.