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MUHAS

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Workshop

Drug lifecycle control in Subsaharan Africa

From production to responsible safe disposal and elimination in wastewater treatment plants

(Med4Africa)

Development of quality herbal medicines in Tanzania: Opportunities and Challenges

Mainen Julius Moshi

Department of Biological and Pre-Clinical Studies, Institute of Traditional Medicine, MUHAS

Drug Life Cycle Workshop – Arusha, Tanzania **29th August 2022**

Outline of the Presentation

- Introduction
- Highlights of researches with potential for developing Herbal Medicines in Tanzania
- Building Capacity for conducting clinical trials on herbal medicines
- Building capacity for producing herbal formulations
- Initiatives to develop African Herbal Pharmacopoeia
- Challenges
- What do we need to facilitate the production of quality herbal medicines?
- Conclusion

Introduction

- In Tanzania traditional medicine is deeply integrated into our cultures and it is the most common form of healthcare (Strangeland *et al*., J Ethnopharmacol 2008;117: 290 – 299)
- The Tanzania Government supports Traditional Medicine practice (TMP) as an important component of healthcare and efforts are in place to integrate TMP into the healthcare system.

- TMP is regulated under the Traditional and Alternative Medicines Act 2002.

- The Tanzania Government in the 2022/23 financial year allocated budget for research in traditional Medicine through the National Institute for Medical Research, part of which was allocated to ITM at MUHAS

Introduction

TMP is supported by other legislations in the areas of medicinal plants including:

- Legislation on conservation of biodiversity
- Legislations on environment, forest, food, agriculture, Intellectual Property Rights, Access and Benefit Sharing

- At the international level Tanzania is a signatory to international conventions, including, the Global Strategy for Plant Conservation (GSPC), the Convention on International Trade in Endangered Species (CITES), the Convention on Biological Diversity (CBD), and the Kyoto Protocol 2010

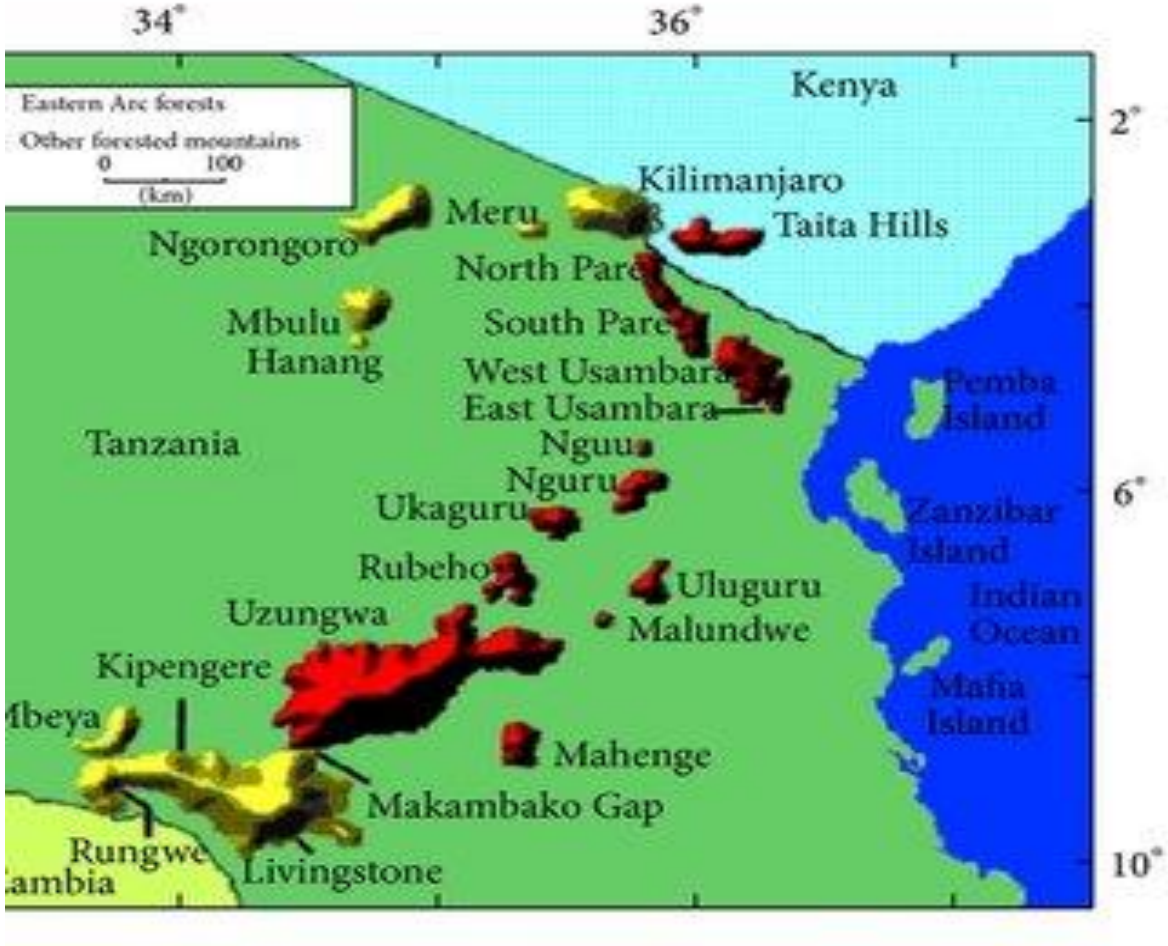
Traditional Medicine Research in Tanzania

- Initially the Institute of Traditional Medicine was the only institution researching into traditional medicine and traditional healing systems in Tanzania
- Currently more stakeholders are involved including the Sokoine University of Agriculture, the National Institute for Medical Research (NIMR), the Department of Chemistry University of Dar es Salaam, the School of Pharmacy (MUHAS) and the Ifakara Health Institute (IHI)

- **Areas of research**:- Phytochemistry, ethnomedical, pharmacological studies(antimalarials, antimicrobials, antidiabetic, antiulcer, larvicidal and insecticidal agents discovery), a few clinical trials, preclinical toxicology etc

Highlights of researches with potential for developing Herbal Medicines in Tanzania

Tanzania, with over 12,000 plant species, is one of international biodiversity hotspots; the Eastern Arc mountains are home to a number of plant species that are endemic and a number of them are used as traditional medicines.

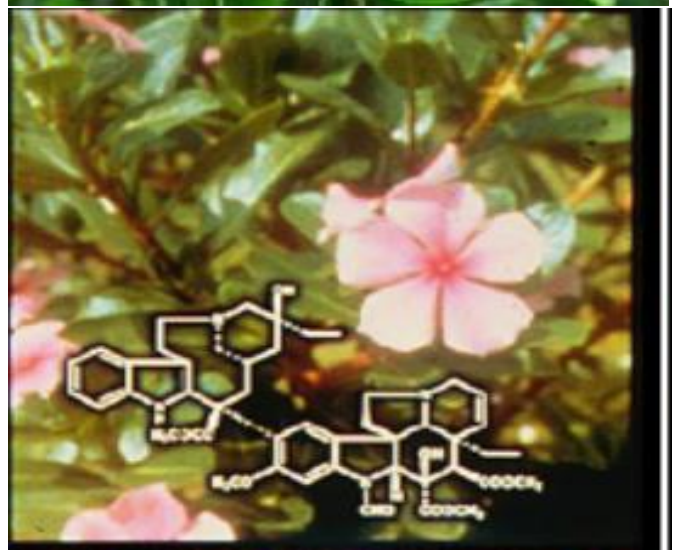


- Nearly 5000 medicinal plant species have been documented since the early 1970s and publications are available **but compilation not yet done**
- A number of plants have been tested for biological activity (> 200 publications since 1997)
- There are a number of these plants whose monographs are included in the WHO monographs, different pharmacopoeia, Indian and Chinese herbal medicines

Highlights of researches with potential for developing Herbal Medicines in Tanzania

Isolation of Anticancer compounds from Tanzanian Medicinal Plants

- *Vinca rosea*/*Catharanthus roseus* L. (the Madagascar periwinkle) is a very common plant that is frequently found in gardens in our homes
- It is the source of the anticancer drug *vincristine* and its derivatives *vinblastine* and *vinerolbine* – **Opportunity to isolate and sell API**



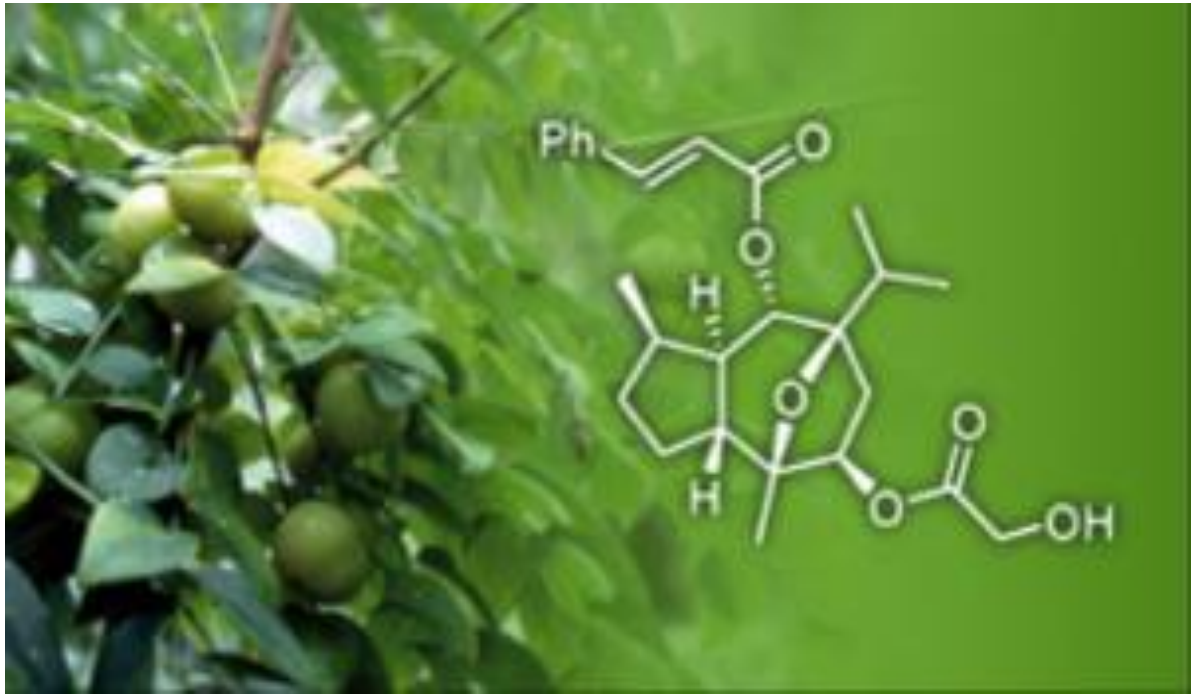
Vincristine

- Our recent studies also provide evidence of plants likely to yield other anticancer compounds (Matata *et al*., 2018; 2020a,b; 2021)

Highlights of researches with potential for developing Herbal Medicines in Tanzania

Isolation of Anticancer Compounds from Tanzanian Medicinal Plants

- *Phyllanthus engleri* collected from Tanzania by the NCI led to the isolation of englerin A (Ratnayake *et al*., 2009), a complex guaiane sesquiterpene which selectively inhibited renal cancer cell line growth but was found to exhibit toxicity. A number of synthetic derivatives have been made with progressively reduced toxicity and higher selectivity (Lopez-Suarez *et al*., 2016; Reagan *et al*., 2019; Schremmer, 2022)



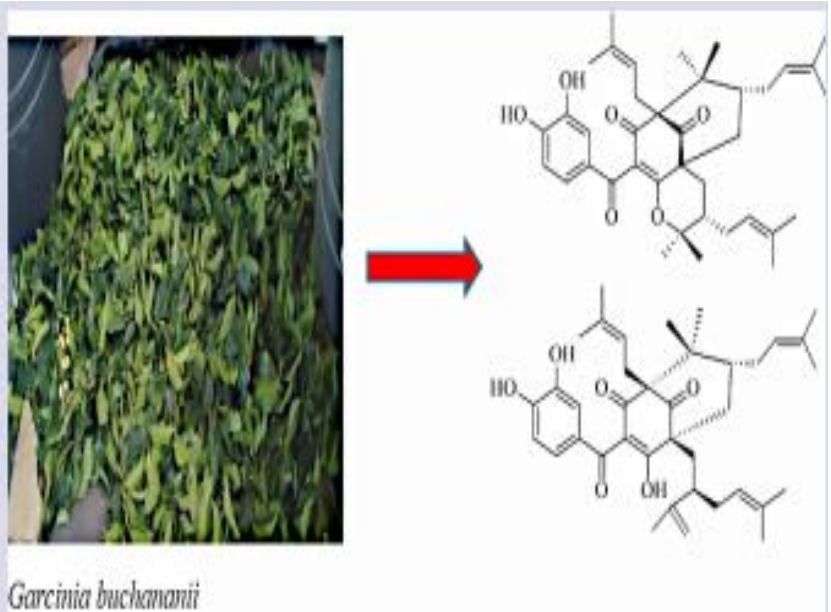
Molecular Structure of (-)- englerin A

Initial anecdotes emanated from research done by the ITM. Moshi *et al*., Afr. J. Trad. CAM (2006) 3 (3): 48 - 58

Highlights of researches with potential for developing Herbal Medicines in Tanzania

Isolation of anti-plasmodial compounds from Tanzanian medicinal plants

- Recently in our labs two compounds were isolated from *Garcinia buchannanii* with antiplasmodial activity; Isogarcinol IC_{50} of 7.0 µg/mL (11.7µM) and 2.8 µg/mL (4.6 µM) against the D6 (CQ sensitive) and W2 (CQ resistant) *Plasmodium falciparum* strains, respectively and Guttiferone F with IC_{50} of 10.6 µg/mL (17.6 µM) and 3.9 µg/mL (6.5 µM) against D6 and W2 strains, respectively (Omole *et al*., Pharmacogn Commn 2019;9: 96-99).



Pharmacogn. Commn. 2019; 9(3): 96-99
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
www.phcogcommn.org

Original Article

Antiplasmodial Biflavanones from the Stem Bark of *Garcinia buchananii* Engl.

Ruth Anyango Omole[1,2,*], Mainen Julius Moshi[1], Matthias Heydenreich[3], Hamisi Masanja Malebo[4], Jeremiah Waweru Gathirwa[5], Richard Owor Oriko[6], Leonida Kerubo Omosa[6], Jacob Ogweno Midiwo[6]

Highlights of researches with potential for developing Herbal Medicines in Tanzania

Isolation of anti-plasmodial compounds from Tanzanian medicinal plants

Phytochemistry Letters 30 (2019) 194–200

Contents lists available at ScienceDirect

Phytochemistry Letters

journal homepage: www.elsevier.com/locate/phytol

Two lignans derivatives and two fusicoccane diterpenoids from the whole plant of *Hypoestes verticillaris (L.F.) Sol. Ex roem. & schult*

Ruth Anyango Omole[a,b,*], Mainen Julius Moshi[a], Matthias Heydenreich[c], Hamisi Masanja Malebo[d], Jeremiah Waweru Gathirwa[e], Sharon Alice Ochieng'[f], Leonida Kerubo Omosa[f], Jacob Ogweno Midiwo[f]

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[d] Department of Traditional Medicine Research, National Institute for Medical Research, P.O. Box 9653, Dar es Salaam, Tanzania
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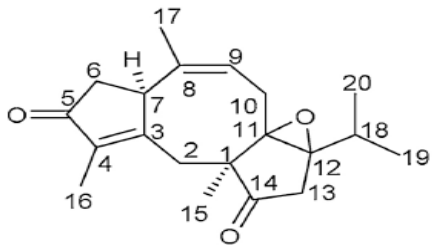
[f] Department of Chemistry, University of Natrobi, P.O. Box 30197, 00100, Chiromo Road, Natrobi, Kenya



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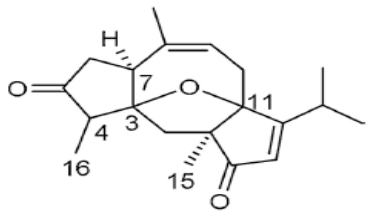
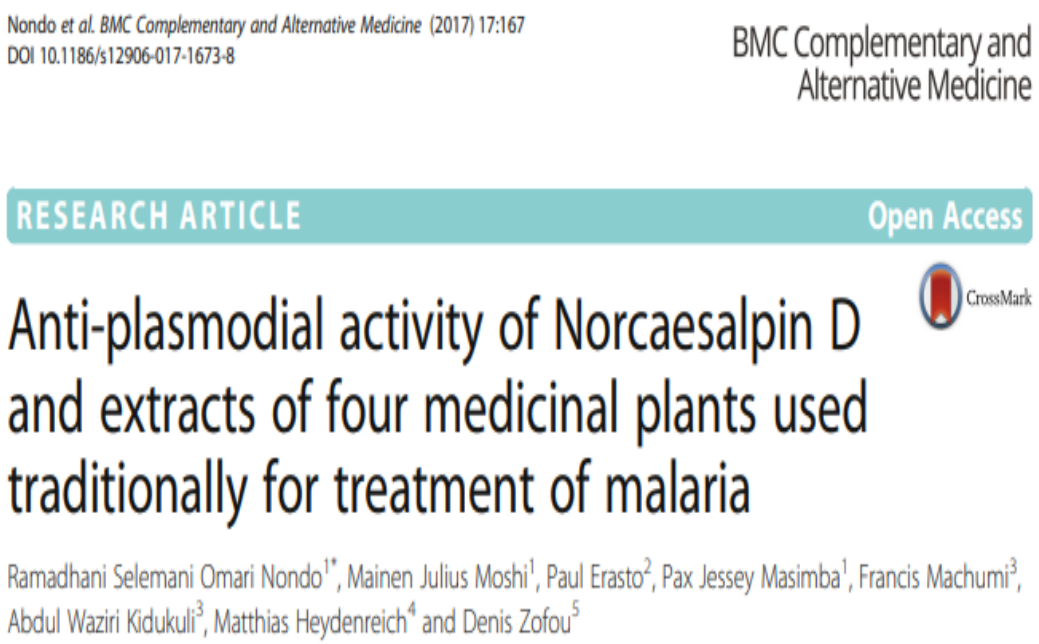


4

Four compounds with antiplasmodial activity were isolated including two fusicoccane diterpenoids: 11(12)-epoxyhypoestenone (**3**) and 3(11)-epoxyhypoestenone (**4**). Compound (**3**) had an IC_{50} of 33 µM against CQ resistant W *Plasmodium falciparum* strain

Highlights of researches with potential for developing Herbal Medicines in Tanzania

Isolation of Anti-plasmodial compounds from Tanzanian Medicinal Plants



Nondo *et al. BMC Complementary and Alternative Medicine* (2017) 17:167
DOI 10.1186/s12906-017-1673-8

BMC Complementary and Alternative Medicine

RESEARCH ARTICLE Open Access

Anti-plasmodial activity of Norcaesalpin D and extracts of four medicinal plants used traditionally for treatment of malaria

Ramadhani Selemani Omari Nondo[1*], Mainen Julius Moshi[1], Paul Erasto[2], Pax Jessey Masimba[1], Francis Machumi[3], Abdul Waziri Kidukuli[3], Matthias Heydenreich[4] and Denis Zofou[5]

- Root ethanolic extracts of *Erythrina schliebenii* IC_{50} 1.85 µg/mL, *Holarrhena pubescens* (IC_{50} 2.05 µg/mL) and *Dissortis melleri* (IC_{50} 2.43 µg/mL)
- Norcaesalpin D isolated from the root extract of *Caesalpinia bonducella* exhibited antiplasmodial activity with IC_{50} of 2.0, 3.9 and 4.5 µM against 3D7, Dd2 and IPC 4912-Mondolkiri strains, respectively (Nondo *et al*., 2017)
- Acute, sub-acute and 90 day toxicity studies done (Sindete *et al*., Hindawi. Evidence-Based Complementary and Alternative 2021, Article ID 6620026. https://doi.org/10.1155/2021/6620026)
- Contemplating to do in human studies.

Highlights of researches with potential for developing Herbal Medicines in Tanzania

Isolation of antimycobacterial compounds

ELSEVIER

Journal of Ethnopharmacology

Volume 296, 5 October 2022, 115501

Safety evaluation and bioassay-guided isolation of antimycobacterial compounds from *Morella salicifolia* root ethanolic extract

Alphonce Ignace Marealle [a, b], Ester Innocent [b], Kerstin Andrae-Marobela [c], Michael Qwarse [d], Francis Machumi [d], Ramadhani S.O. Nondo [b], Matthias Heydenreich [e], Mainen Julius Moshi [b]

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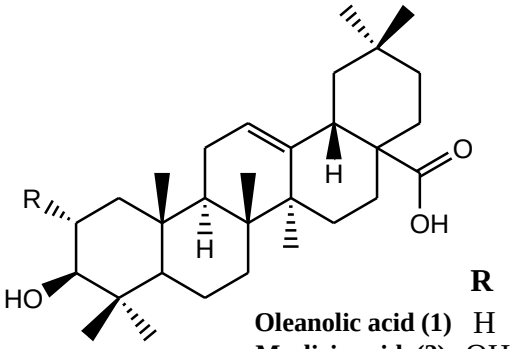
[b] Department of Biological and Pre-clinical Studies, Institute of Traditional Medicine, Muhimbili University of Health & Allied Sciences, Dar es Salaam, Tanzania

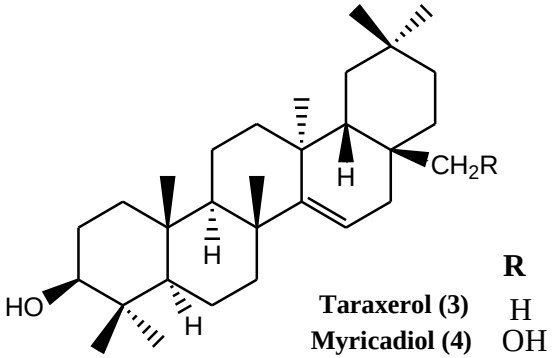
[c] Department of Biological Sciences, University of Botswana, Garborone, Botswana

[d] Department of Natural Products Development and Formulations, Institute of Traditional Medicine, Muhimbili University of Health & Allied Sciences, Dar es Salaam, Tanzania

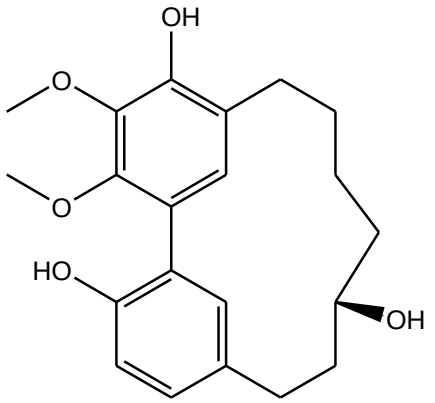
[e] Institute of Chemistry, University of Potsdam, Potsdam, Germany



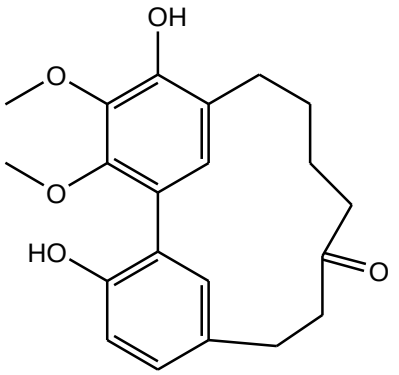
	R
Oleanolic acid (1)	H
Maslicic acid (2)	OH



	R
Taraxerol (3)	H
Myricadiol (4)	OH



(±)-Myricanol (5)

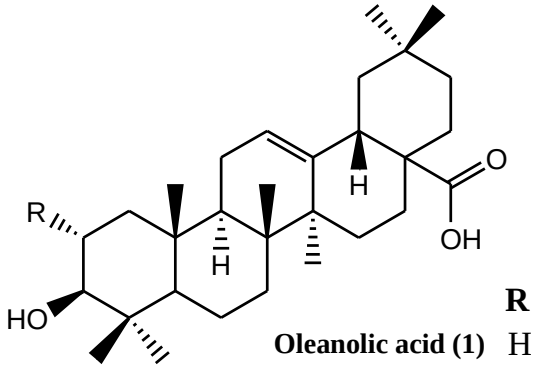


Myricanone (6)

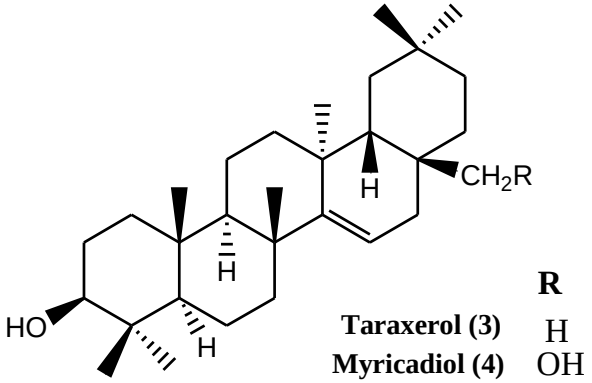
Highlights of researches with potential for developing Herbal Medicines in Tanzania

Isolation of antimycobacterial compounds

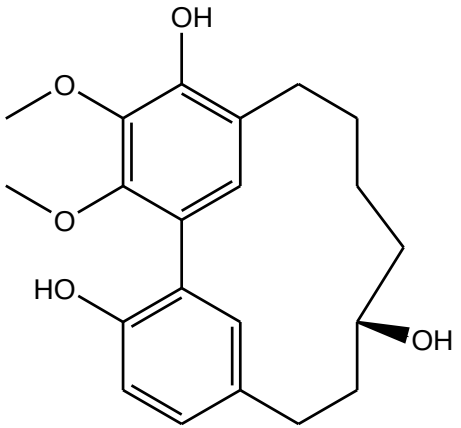
- The six cpds exhibited activity against 3 non-pathogenic mycobacteria species.
- Compound **(2)** was the most active with MICs of 17, 28 and 56 µg/ml against *M. tuberculosis* strain $H_{37}R_V$ and rifampicin resistant *M. tuberculosis* clinical isolates, respectively.
- Crude extract exhibited a good safety profile in preliminary results



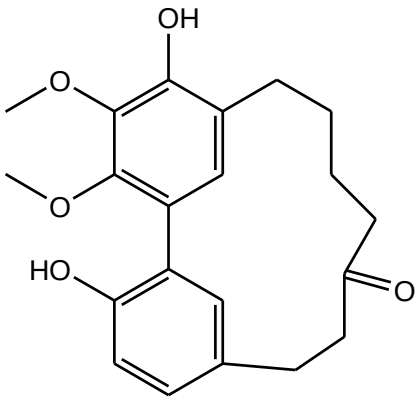
	R
Oleanolic acid (1)	H
Maslicic acid (2)	OH



	R
Taraxerol (3)	H
Myricadiol (4)	OH



(±)-Myricanol (5)

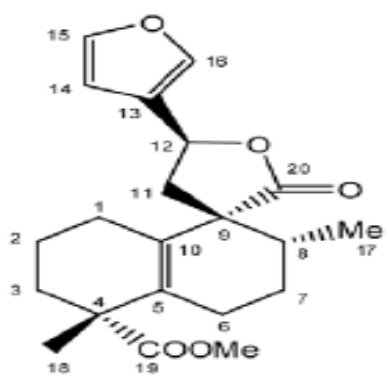


Myricanone (6)

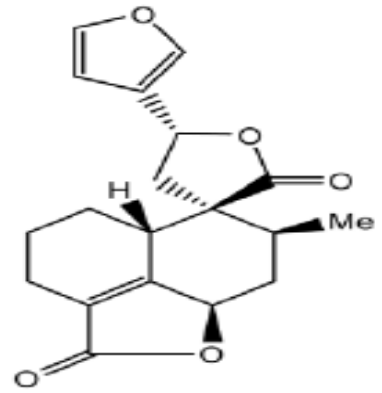
Highlights of researches with potential for developing Herbal Medicines in Tanzania

Isolation of antifungal compounds from *Croton jatrophoides* Pax

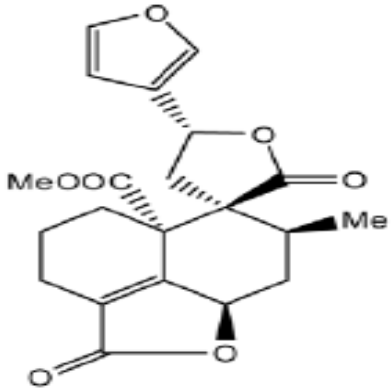
MIC	µg/ml	µg/ml
SAMPLE	***Candida albicans***	***Cryptococcus neoformans***
Cpd (1)	6.25	12.50
Cpd (2)	3.125	6.25
Cpd (3)	3.125	6.25
Clotrimazole	0.19	0.19



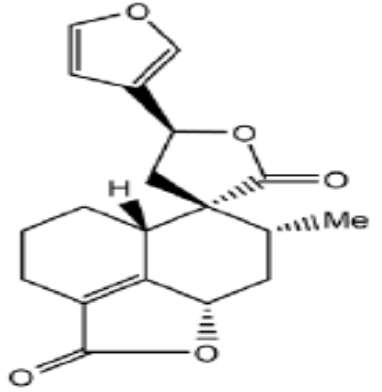
Penduliflaworosin (**1**)



Isoteucvin (**2**)



Jatrophoidin (**3**)



Teucvin (**4**)

Other existing opportunities and low hanging fruits

Tanzania has many plants with already established therapeutic value which can be exploited for local APIs, FPPs production or for sale to industry else where e.g.

- *Agave sisalana* – hecogenin;
- Avocado (*Persea Americana*) – β-sitosterol;
- Amaranthus spinosa – β-sitosterol; *Prunus Africana* – triterpenes (– β-sitosterol); *Eucalyptus globulus* – menthol
- Acacia species – gum arabica
- Tea tree oil - antiseptic

Other existing opportunities and low hanging fruits

- *Allium Ceppa* (Onion): has antiviral, anti-inflammatory, antithrombotic effects (Dorsch et al., 2021)
- *Aloe vera* and Tea tree oil: Antiseptic properties make them useful for inclusion in hand sanitizers
- Curcumin, the main phytochemical of Tumeric (*Curcuma longa* L.): Has potential immune-boosting properties; it is a potent antioxidant and stimulates the production of interferons to activate the host innate immunity.
- Garlic (*Allium sativum* L.): Suppresses production and secretion of proinflammatory cytokines and boosts immune system cells. Stimulates NK cells, T and B lymphocytes, eosinophils, and macrophages by modulation of immunoglobulin synthesis, phagocytosis, and macrophage activation, and cytokines secretion.

Building Capacity for conducting clinical trials on herbal medicines

- It has taken a long time for clinicians to accept collaboration with researchers in traditional medicine
- The first ever clinical trial in this area was conducted in 2002 and results were published in Phytotherapy Research (Moshi *et al*., 2004)
- In about the same period a postgraduate doctor in surgery did a clinical trial of *Prunus Africana* L. bark extract for management of benign prostatic hypertrophy
- Recently a clinical trial on malaria has been in progress and part 1 of the study on dose escalation and tolerability is completed (Kamaka *et al*., in Press)

PHYTOTHERAPY RESEARCH
Phytother. Res. **15**, 577–580 (2001)
DOI: 10.1002/ptr.780

The Effect of *Phyllanthus amarus* Aqueous Extract on Blood Glucose in Non-insulin Dependent Diabetic Patients

Mainen J. Moshi,[1]* Janet J. K. Lutale,[2] Gerald H. Rimoy,[3] Zulfikar G. Abbas,[2] Robert M. Josiah[2] and Andrew B. M. Swai[2]

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The glycaemic response to 124.5 ± 9.3 (mean ± SD) g of pancakes was monitored in 21 non-insulin dependent diabetic (NIDDM) patients while on oral hypoglycaemics, after a 1-week washout period and after a 1-week twice daily treatment with 100 mL of an aqueous extract from 12.5 g of powdered aerial parts of *Phyllanthus amarus*. After the 1-week washout period, the fasting blood glucose (FBG) and post-prandial blood glucose increased significantly compared with treatment on oral hypoglycaemics ($p < 0.05$). After a 1-week herbal treatment no hypoglycaemic activity was observed. Both FBG and post-prandial blood glucose remained very similar to that recorded after the washout period ($p > 0.05$). Both liver and renal functions based on alanine transaminase (ALAT) and serum creatinine, respectively, were not significantly affected by the use of the extract. Although the lymphocyte and monocyte levels were significantly decreased ($p < 0.05$) and the granulocyte level was significantly increased after treatment ($p < 0.05$) the overall total white blood cell (WBC) count and haemoglobin (Hb) were not significantly affected by the 1 week herbal treatment. We conclude that 1 week treatment with the aqueous extract of *Phyllanthus amarus* was incapable of lowering both FBG and postprandial blood glucose in untreated NIDDM patients.

Keywords: Phyllanthus amarus; euphorbiaceae; aqueous extract; NIDDM; treatment.

Building Capacity for conducting clinical trials on herbal medicines

Preclinical Studies:

- The Department of Pathology has sustained keen interest in supporting preclinical safety evaluation as evidenced by some already published results of work which was done in collaboration with the ITM
  -Francis P *et al*., Tanzania Journal of Health Research 2018;20: 1-8.
  - Mwakigonja *et al*., J Adv Sci Res, 2018, 9 (2): 26-33

We need to ride on this wave to achieve a full cycle development and bring evidence-backed herbal formulations to the table

Building capacity for formulations development

- The Institute of Traditional Medicine (MUHAS) has ventured into developing 19 herbal formulations and gradually standardization is in progress; a few have already been registered by the TMDA. Sale of herbal products generates income for the Institute
- Efforts are underway to mount a Masters program in standardization of herbal medicines
- Currently a few students on the MSc Trad Med Dev program have done their projects on standardization as part of seed capacity development

Utilization of the existing potential in Tanzania

- The few examples highlighted above are potential areas for further development including safety evaluation, isolation and conduct of structure activity relationship studies

- Some initiatives to expedite formulation of standardized extracts are envisaged which will be followed by clinical trials upon availability of adequate safety evaluation data

- Partnerships for synthetic modification of isolated compounds with reasonable activity may be a good direction to take

Utilization of the existing potential in Tanzania

- Unlike other cultures in the world e.g. Unani, Ayurveda, Chinese, etc, traditional medicine in Tanzania and most of Africa is scantly documented

- Documentation is a very recent development in our histories which weaken initiatives on valorization of this important resource

- While some documentation of Tanzanian plants used in TMP has already been done we are lagging behind in the development of monographs to guide production of quality herbal medicines

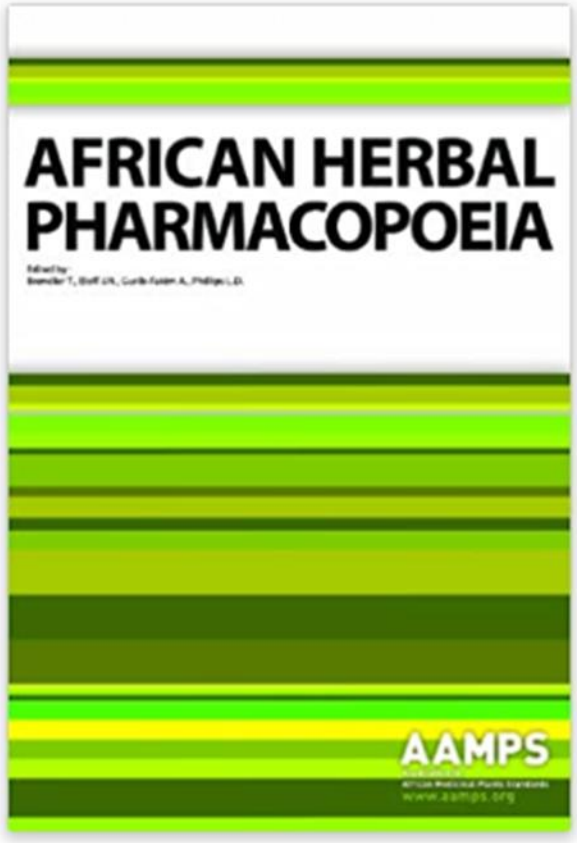
Initiatives to develop African Herbal **Pharmacopoeia**

- This is an important initiative directed at promoting research, support plant material collectors, industrial production of herbal medicines and consequently commercial cultivation of medicinal plants

- In 2005 the African Association for Medicinal Plants Standards (AAMPS) was initiated consisting of experts in the area of herbal medicines with the purpose of promoting industrial production of African medicinal plants products.

- The AAMPS which has its headquarters in Mauritius has developed an African Herbal Pharmacopoeia.

Initiatives to develop African Herbal Pharmacopoeia

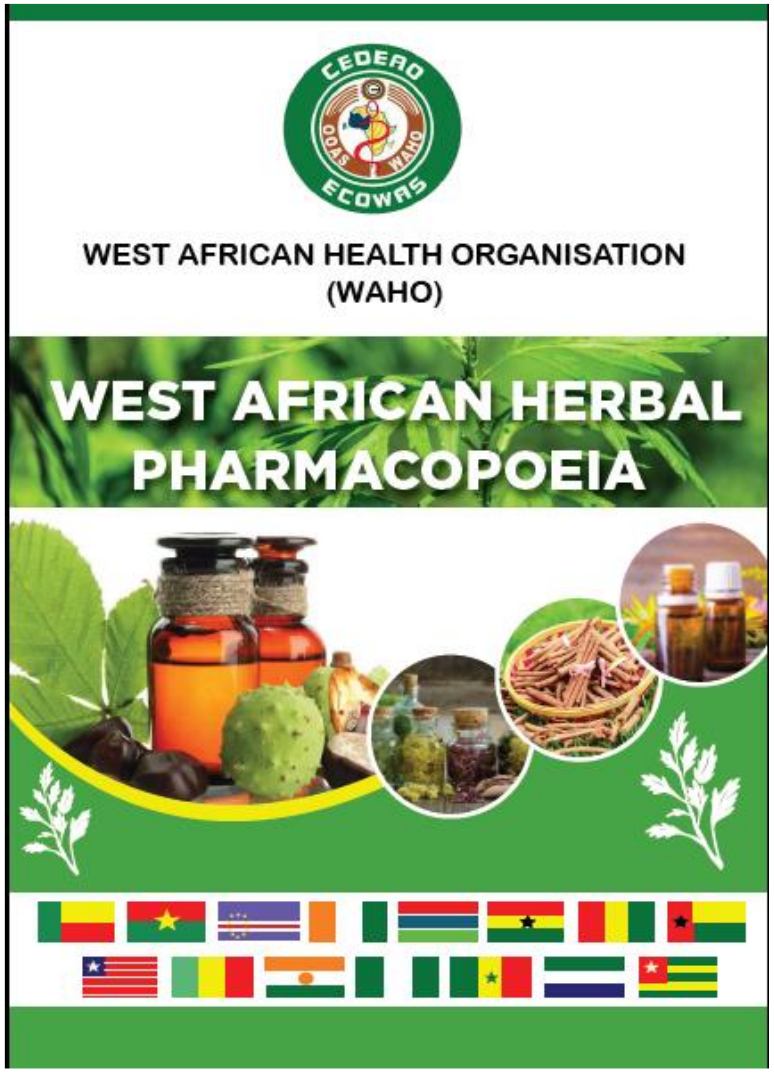


- The Pharmacopoeia provides detailed and current botanical, phytochemical and commercial information on 51 important African medicinal plants.

- Information covered includes microscopic features of the plant material, HPLC profiles, TLC chromatograms of adulterants, and distribution maps.

- Some of the included monographs of African medicinal plants include *Catharanthus roseus, Cryptolepis sanguinolenta*, *Hoodia gordonii, Prunus africana, Harpagophytum procumbens, Pelargonium sidoides* and *Sutherlandia frutescens* (Marston A. Review of the African herbal pharmacopoeia. J Altern Complement Med 2011;17:571).

Initiatives to develop African Herbal Pharmacopoeia

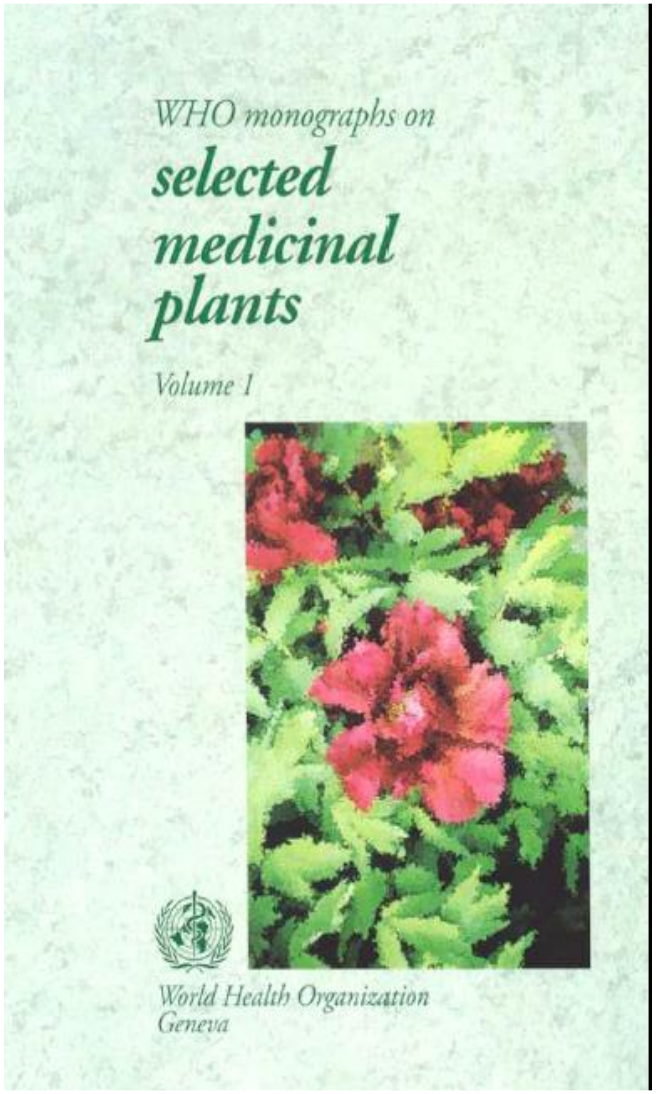


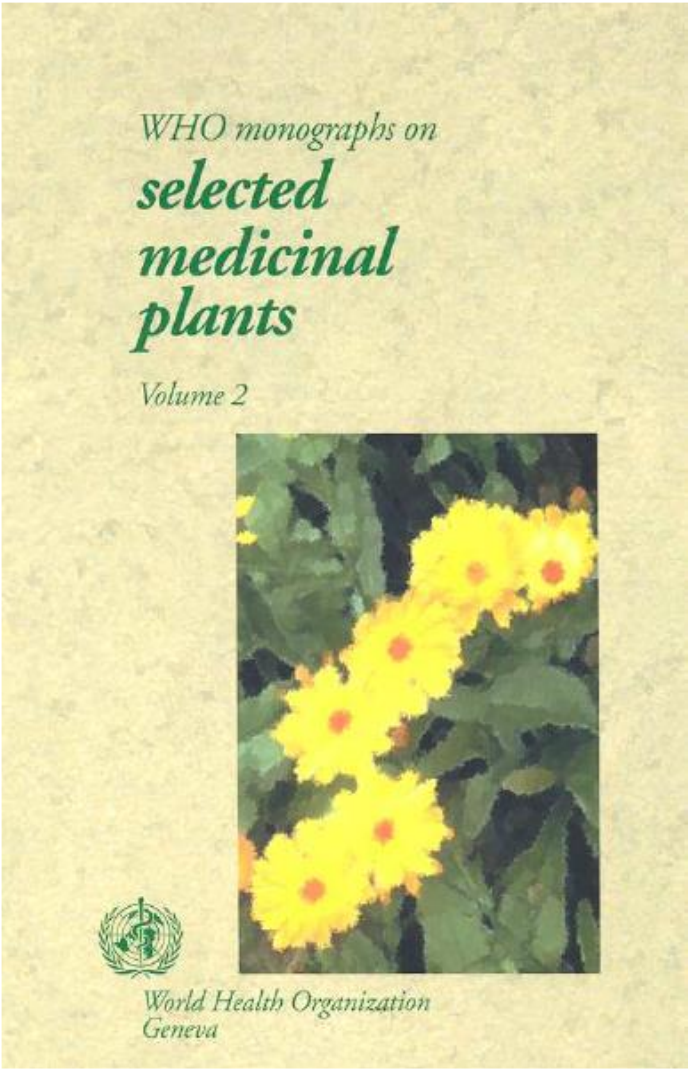
- In West Africa a Pharmacopoeia was developed by the West African Health Organization (WAHO): West African Herbal Pharmacopoeia (2013), which has monographs for 31 medicinal plants.

- Almost all 31 plants in the West African Herbal Pharmacopoeia grow in Tanzania

Initiatives to develop African Herbal Pharmacopoeia

- The WHO has published Monographs of Medicinal Plants
- Part 1 has monographs for 26 Medicinal plants
- Part 2 has monographs for 26 medicinal plants
- Again several plants in the two monographs are found in Tanzania, hence creating good stepping stones for moving forward





Challenges

- Like in many other African countries, Tanzania loses extensive areas of forests due to expansion of human settlements, agricultural activities, forest fires, tree felling for timber, international trade, and refugees activities.

- Harvesting of medicinal plants from the wild by traditional health practitioners has a big impact as there is no guarantee that they will practice sustainable harvesting.

- Weak enforcement of existing legislations is a major contributor to lose of plant biodiversity in the form of illegal timber and medicinal plants trade.

Characteristics of the Tanzanian ecological zones; botany and medicinal plants (MPs)

Ecological zone	% of total land area	% area within PAs	Biodiversity quality and MP richness	Relative change
Z I: moist forest mosaic	4.4	12.0	Rich in plant sp.; poor in endemic plants	Heavy human pressure due to cultivation, grazing and fuelwood; more than 20% of forest area has been lost
Z II: coastal forest	6.2	21.2	Rich in plant species and MPs rich, 600 endemic sp., habitat fragmentation threatens species survival	Over 90% of original forest destroyed; many FRs is too small to be viable as PAs
Z III: mountain forest	6.0	27.7	Rich in flora and MPs, of the 4,000 plant species, 75% endemic; 1/5 of tree sp also endemic	More than 70% of land outside PAs is converted to farmland, grazing or is degraded
Z IV: acacia-Savannah Grassland	18.1	41.4	Moderately rich in flora and MPs, 2500 species of plants	Extensive areas outside PAs suffer severe deterioration due to overstocking
Z V: acacia-Commiphora Thornbush	7.2	37.2	Moderately rich in flora, 2500 sp. of plants of which 50% are endemic	Extensive areas outside PAs suffer severe deterioration due to overstocking
Z VI: brachystegia-Jubernadia Woodland (Miombo)	58.1	46.7	Very rich in flora and MPs, 8500 sp. of plants of which 54% are endemic; famous for fine hardwoods	Over 20% of woodland has been converted to farmland, grazing or degraded; extensive deforestation for charcoal, fuel wood and overgrazing occurs

Adapted from: Stuart et al. (1990) and Clark (1995) in GURT (1998) GURT (Government of the United Republic of Tanzania) 1998.

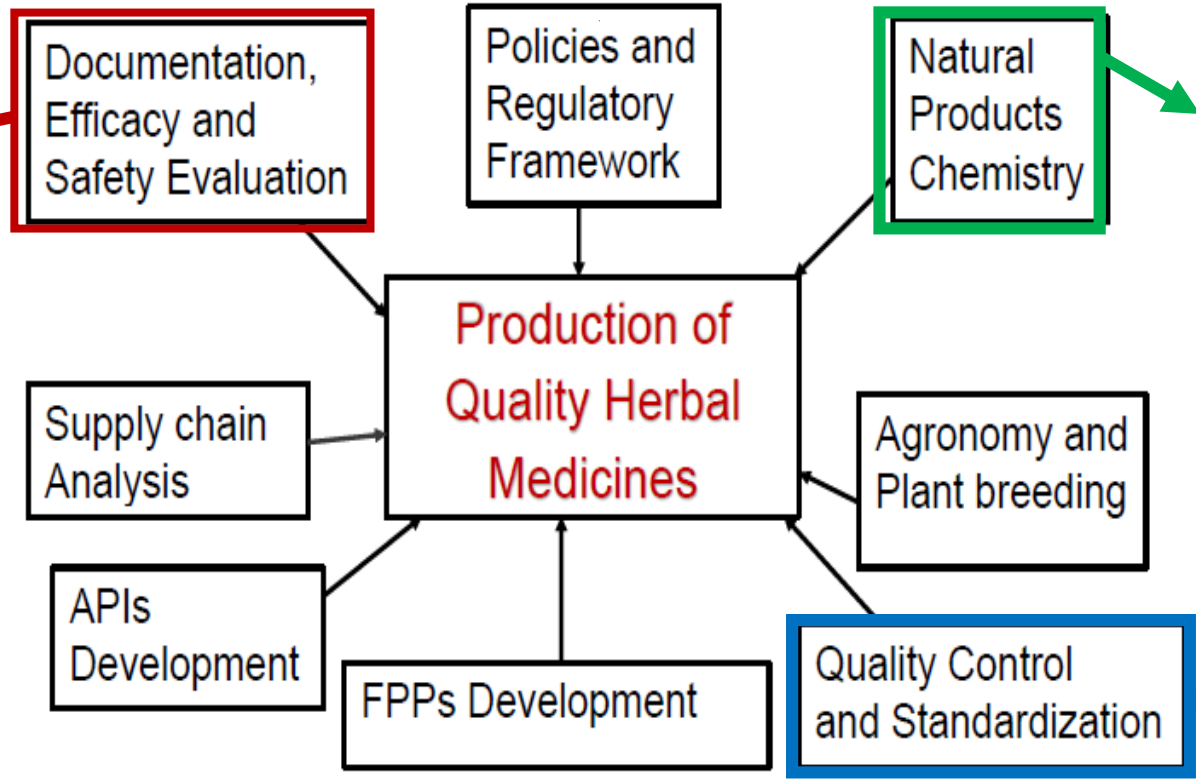
Strangeland *et al*., J Ethnopharmacol 2008;117: 290 – 299

Challenges

- Scattered efforts on cultivation exist for some plants but none at a significantly large commercial scale
- Weak linkage between industry and academia
- Inadequate human resource capacity in strategic disciplines needed for producing quality herbal medicines
- Inadequate research and production infrastructure

What do we need to facilitate the production of quality herbal medicines?

- Mount a large documentation initiative of Tanzanian medicinal plants
- Promote enhanced evaluation for safety and efficacy

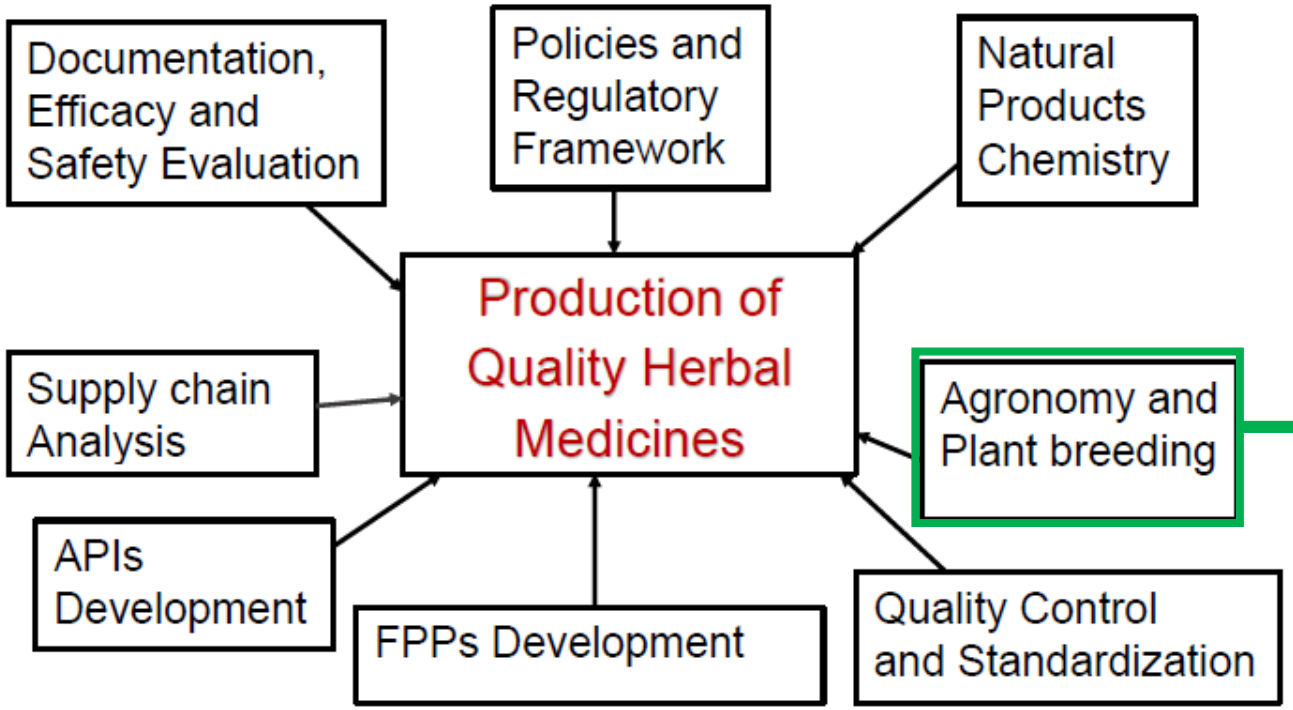


The Herbal Medicines Production Ecosystem

- Expand capacity for natural products chemistry and launch campaign for development of standardization markers

- Develop monographs
- Invest in analytical equipment

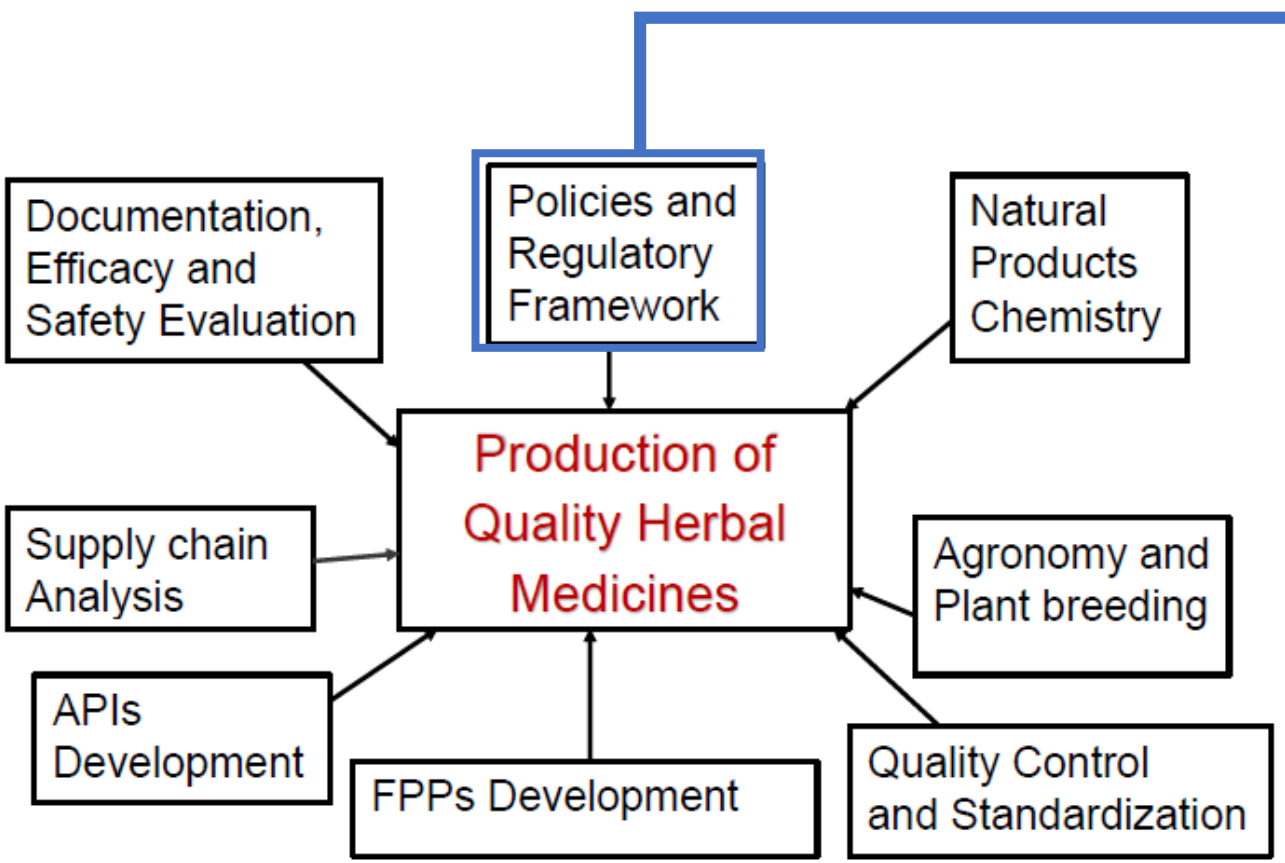
What do we need to facilitate the production of quality herbal medicines?



The Herbal Medicines Production Ecosystem

- Establish collaborations between Agriculture, forestry, Tanzania seed company, farmers
- Develop commercial farming for medicinal plants
- Build strong capacity for tissue culture and plant breeding to ensure sustainable harvesting

What do we need to facilitate the production of quality herbal medicines?

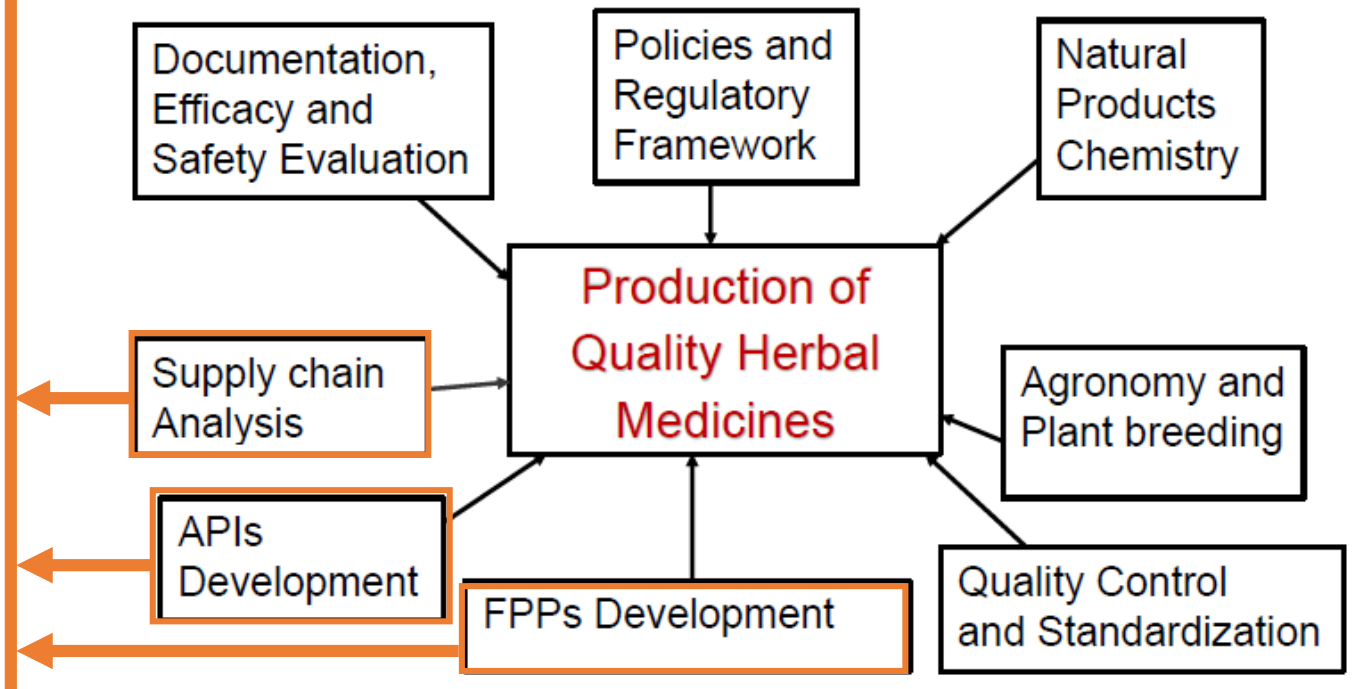


The Herbal Medicines Production Ecosystem

- Harmonize existing policies to facilitate sustainable herbal medicines exploitation
- Strengthen regulatory framework and guidelines for registration of herbal medicines
- Address conflicting areas in existing laws to strengthen their enforcement

What **do** we need to facilitate the production of quality herbal medicines?

- Build capacity for APIs development through synthetic modification of isolated active molecules
- Provide at national level resources for patenting commercially promising cpds
- Create a conducive environment to enable engagement of local pharmaceutical industry in this area such as tax rebate
- Address supply chain issues including managing competition by similar imported products



The Herbal Medicines Production Ecosystem

Conclusion

There are high hopes that in Tanzania we may now make progress towards production of herbal medicines but we:

- We have a better chance if we capitalize on already known plants
- Need to mobilize/allocate resources and investment in capacity building
- Should make Regulatory and Policy interventions in areas affecting sustainability of the supply of herbal raw materials, patenting and registration of herbal medicines, FPPs and APIs
- Need to review the National Research Policy to make provisions that enable creation of a strong linkage between industry and academia