Traditional Medicine Partnerships – For Drug Discovery, Healthcare and Capability Strengthening

Indigenous Bioresources Research Group (IBRG)

Co-directed by A/Prof Subra Vemulpad (medical microbiologist)

Work in partnership with Indigenous people being guided by their needs
- document and preserve first hand traditional medicinal knowledge
- Chemical and biological investigations with a focus on plants used for skin infections, sores and wounds, some cancers
- provide capability strengthening opportunities for our Indigenous partners

All IBRG research is community directed, following specific requests of our Indigenous partners
Overview

• Importance of traditional medicinal knowledge
• Research we (IBRG) undertake
• Collaborative partnership with Indigenous people on ‘bush medicines’ research – capability strengthening

Traditional Medicines

• The World Health Organization (WHO) defines traditional medicine as:

“... the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, ... used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.”

• ~80% of the population in developing countries still rely on traditional medicines as primary healthcare

See http://www.who.int/medicines/about/en/
Traditional Medicinal Plants in Drug Discovery

- Plant-based traditional medicines are the most consistently successful source of novel drugs
- ~80% of all plant-derived drugs in current use globally were discovered from the study of traditional medicines
- Traditional medicines are associated with a high hit rate of non-toxic bioactive molecules
- Major resource for safe medicines and the discovery of new drug-like molecules


Traditional Medicinal Plants in Drug Discovery

- Artemisinin (qinghaosu) - isolated from the herb Artemisia annua
- Used for more than 2000 years as a herbal tea against fever and chills
- Potent antimalarial agent - treatments containing artemisinin derivatives (artemisinin-combination therapies, ACTs) are now the standard treatment worldwide for Plasmodium falciparum (malaria)
Australian Aboriginal ‘Bush’ Medicines

- Australian Aboriginal people have used plants as medicines (bush medicines) for thousands of years
- Have a vast knowledge of the traditional use of their flora, many of which are endemic to Australia and specific regions
- Medicinal use is especially still dominant in remote Indigenous communities

Fabricant & Farnsworth, Environ Health Perspect, 2001, 109, 69

NSW Bush Medicines

- We reviewed literature on 128 traditional medicinal plants of NSW
- Referred to as customary medicines in recognition of Australian Aboriginal medicinal use evolving to incorporate traditional and modern knowledge and practices
- Plant genera Acacia, Corymbia, Eucalyptus, Eremophila, and Melaleuca are most commonly used

Packer et al, Medicinal plants of New South Wales, Australia, in Genetic Resources, Chromosome Engineering, and Crop improvement: Medicinal Plants, Singh, 2012, 259
NSW Bush Medicines

• Plant material is often
  - crushed, heated and used as topical poultice
  - infused or decocted in hot/boiling water or
    macerated in cold water and applied topically or
    rubbed into the skin

• Plant material may also be less
  commonly inhaled or drunk as a decoction

• Plants are also used directly as
  the sap topically, and orally by
  chewing leaves and twigs, or
  eating fruits

Traditional Medicine Partnerships – J Jamie

No 9

NSW Bush Medicines

• Plant material commonly been used to treat sores and
  skin complaints, toothache, coughs and congestion,
  sore ears and eyes, stomach aches, diarrhoea and
  constipation, fevers, and aches and pains

• Wide range of biological activities - most frequently
  reported are antibacterial, anti-inflammatory and
  antioxidant activities

• Great diversity in the types of natural products that have
  so far been isolated

• For many plants, the biological activities and bioactive
  compounds isolated are aligned with customary
  medicinal uses

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No 10
NSW Bush Medicines

- *Melaleuca alternifolia* (tea tree) - customarily used for treatment of abrasions, cuts, and sores
- Well known for its antibacterial and anti-inflammatory properties, which are attributed especially to terpenes and terpenoids present in its essential oil
- Many of the NSW medicinal plants documented have also been used as traditional medicines in various parts of the world for similar ailments

Bush Medicines

- Customary medicinal knowledge is of cultural value and of significant potential in healthcare and drug discovery
- BUT rapidly disappearing, due to deaths of the Elder custodians and communities being dislocated and westernised
- Efforts need to be made to conserve this important knowledge and understand its medicinal significance for the wellbeing of Indigenous and non-Indigenous people and biodiversity significance
Bush Medicines

• WHO - maintenance of Indigenous peoples’ ethnobiological knowledge is a priority area, along with development of proactive policies to strengthen role that traditional/customary medicine plays in keeping populations healthy
• The Australian Federal government in Australia’s Biodiversity Conservation Strategy 2010-2030 acknowledged maintenance of Indigenous peoples’ traditional knowledge is a priority and that it is essential to be done with the active engagement of Indigenous people
• Role of IBRG to conserve customary knowledge, understand medicinal properties biologically and chemically and give back to community to help in wellbeing

Customary Medicines Partnerships

• Strong collegial partnerships with Indigenous people on customary knowledge for cultural preservation, bioactive discovery from plants and capability strengthening
• Elder Indigenous custodians integral to entire project
IBRG Methodology

• Follow ethical guidelines of NH&MRC and UNESCO
  - Indigenous people are research partners

• Collaborative agreements
  - ownership of customary knowledge respected
  - joint ownership of results
  - benefit sharing and capability strengthening essential


NH&MRC. Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research.
People, Plants & Protected Areas: A Guide to In Situ Management, 2001, Earthscan

Ethnobotanical Study
(document and preserve)

• Elders interviewed
  – written, oral, video recordings, databases
  – customary preparations, application method, ailments treated
• Aids used to identify specific ailments

*Ethnobotany (from "ethnology" - study of culture and "botany" - study of plants)
Chemical and Biological Studies
(isolate and identify bioactives)

- Plants of potential antimicrobial/anti-inflammatory/anticancer activity our focus
  - plants collected from field
  - crude extracts prepared analogous to customary method

- Customary preparations assayed as appropriate to use
  - antimicrobial assays (bacterial and fungal), skin assays - healing of sores, skin irritations, skin infections
  - antiinflammatory assays - decreasing swelling, redness, pain
  - antiproliferative assays – treating cancers
- Bioassay guided fractionation of active customary preparations to isolate bioactives
Major Partnerships

Yaegl Aboriginal people of NSW

Siddha medical practitioner

Chungtia Village Nagaland

Partnership with Siddha Practitioner

• Siddha is an ancient medical systems of India
• Dr Velmurugan has over 30 years of clinical experience using Siddha medicine to treat cancers and conditions related to inflammation
• Contacted IBRG to undertake chemical and biological studies of his Siddha medicinal plants

*some plants kept confidential as part of collaborative partnership
IBRG-UK-001 – a Siddha Medicine

- A mixture of dried root and leaf powder used by Dr Velmurugan to treat cancer patients – taken orally in form of capsules
- Plant has been used traditionally elsewhere to treat swelling and fever
- No previous reports on uses for treatment of cancers

- 70% aq. EtOH extract with SKNMC (human neuroblastoma cell line) gave antiproliferative activity IC$_{50}$ 22 µg/ml
- Doxorubicin, IC$_{50}$ 0.12 µg/ml
- NCI regards crude extracts IC$_{50}$ < 30 µg/ml as promising (Johkadze et al., Phytother. Res., 2007)

IBRG-UK-001 – a Siddha Medicine

- Crude extract partitioned with n-hexane, EtOAc, n-BuOH, H$_2$O
- H$_2$O showed best activity, IC$_{50}$ 21 µg/ml
- Subjected to bioassay guided studies - RP-HPLC, LH-20 SEC and spectral analysis

First report of scutallarein, apigenin 7-O-β-D-glucoside from plant All compounds known for anticancer activity – supports Dr Velmurugan’s use

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Partnership with Chungtia Elders

- Nagaland lies within the Indo-Burma biodiversity hotspot
- Meyanungsang (Meza), a Chungtia man, contacted IBRG to undertake a PhD on the traditional medicinal plants of his village, with his Elders approval
- Established collaborative partnership, conducted ethnobotanical, biological and chemical investigations
- Helped document and preserve the knowledge and support the medicinal use of these plants by his village
- Culminated in Macquarie University Research Award in "Excellence in External Research Partnership"
- First PhD Dr of his village

Ethnobotanical Documentation

- Interviews were conducted in Chungtia village with 10 Elder custodians of traditional knowledge
- Resulted in the documentation of 135 medicinal plants comprising of 69 families and 123 genera
- Bush medicine handbook developed and journal article

Kichu et al., J Ethnopharmacol, 2015, 166, 5-17
Ethnobotanical Documentation

- Gastrointestinal problems such as stomach ache, dysentery/diarrhoea, constipation, gas formation, gastritis and indigestion
- Skin related treatments such as sores, cuts and wounds (e.g. tiger bite), fungal infection and burns

Antibacterial Screening

- 70% aq EtOH extracts of plants used for skin related treatments selected for antibacterial screening with MTT assay, disc diffusion assays
- Bioassay guided isolation of bioactive compounds from several plants
**IBRG-M-04 Compounds and Activity**

Isoflavones

- C-2: chandalone
  - Not active @ 25 µg/mL

- C-4: alpinum isoflavone
  - MIC: 31.25 - 62.5 µg/mL

- C-7: lupalbigenenin
  - MIC: 9.38 – 18.75 µg/mL

Pterocarpans

- C-6: (S,S)-erythrabyssin II
  - MIC: 31.25 - 62.5 µg/mL

- C-5: 1-methoxyerythrabyssin II
  - MIC: 250 µg/mL

- C-9: phaseollidin
  - MIC: 100 µg/mL

- C-10: cristacarin
  - MIC: 62.5 - 125 µg/mL

Flavanones

- C-1: 5-hydroxysophoranone
  - MIC: 62.5 - 250 µg/mL

- C-8: erytagallin A
  - MIC: 31.25 - 250 µg/mL

- C-3: maackiaflavanone B
  - MIC: 100 µg/mL

Chloramphenicol:

- MIC: 31.25 µg/mL (+ve control)

**IBRG-M-04 Compounds**

**C-2, C-3: first report from this genus**

- C-2: chandalone
- C-3: maackiaflavanone B
- C-4: alpinum isoflavone

**C-4, C-5, C-6, C-7: first report from this species**
IBRG-M-04 Compounds

C-9, C-10, C-11 are new for this species

all the compounds except C-3 have been reported for antimicrobial activity
Ethnobotanical Documentation

- 19 Elders interviewed leading to discussions on 32 medicinal plants from 21 families

Co-authored Publications

- *Journal of Ethnopharmacology* - An ethnobotanical study of medicinal plants used by the Yaegl Aboriginal community in northern New South Wales, Australia, 2012
- *Yaegl Medicinal and Plant Resources Handbook 2011*
Biological Testing of Yaegl Plants

- Tested Yaegl medicinal plants used for treatment of skin infections, sores and wounds and as antiseptics
- Found several plants with high levels of antibacterial activity
- Highly supportive of their medicinal use, highlighting the value of this medicinal plant knowledge of the Yaegl elders

Chemistry investigated - biologically active compounds identified

Alphitonia excelsa (soap tree)

- Leaves of Alphitonia excelsa used by Yaegl community, and other Aboriginal communities, as an antiseptic handwash and for sore eyes
- Leaf extracts (and fractions therein) have shown promising antimicrobial activity against S. pyogenes and resistant strains of S. aureus as well as anti-inflammatory and antioxidant activities
- Bioassay guided isolation studies have led to the isolation of bioactive flavonoids
Database for Preservation

Wellbeing of Indigenous People

- Confirmation of medicinal value of customary medicines to wider scientific community and Western agencies, provides enormous ownership and pride within Indigenous people
- Documentation and scientific support of benefits enables informed decisions to be made about what medicine or combination to employ, empowering local health agencies
- Indigenous people often prefer their customary medicines, especially in remote communities
Wellbeing of Indigenous People

- Opportunities for economic wellbeing
  - Ecotourism
  - Healthcare products

- Preservation of customary medicinal practices and encouragement of their use in healthcare is an important route to closing the gap

Capability Strengthening Opportunities

- Yaegl Elders requested that the IBRG, as scientists and educators, assist with strategies to increase educational outcomes of their local youth
- Led to the National Indigenous Science Education program (NISEP), with the Yaegl Elders as partners
- Places Indigenous school students in leadership positions while promoting science and further education options to these students and the wider community
Science Shows

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Measurable Change

- Since 2008 Maclean High School in Yaegl country has had almost 100% retention rate from the school certificate (Year 10) to Year 11 and 12 (~double the national average)

- Indigenous student demonstrators now in leadership roles eg captain and vice-captains in school and going to university
Cultural Immersion Program 2010 -

- Yaegl elders developed program for Year 7 Maclean High School students
- Elders show to the students on Country important cultural sites, bush foods and bush medicines
- Over 1000 Year 7 students have participated
- Developed enormous respect for Yaegl elders from community and sense of pride in elders

Recognition and pride
Summary

- Traditional/customary medicines is an important resource for cultural, educational, healthcare and economic benefit
- Established excellent partnerships with Indigenous people, with research being guided by their requests
- Undertaken ethnobotanical studies that preserve valuable customary knowledge and chemical and biological studies that support customary uses
- Have provided capability strengthening opportunities

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