

Phytopharmacology

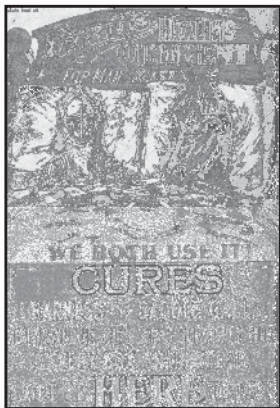
Block 18c



Prof Vanessa Steenkamp

Background

- Plants have formed the basis of traditional medicine systems that have been in existence for thousands of years
- Continue to provide mankind with new remedies
- 2600 BC *Cedar* spp., *Cypress* spp., Licorice, Myrrh, poppy juice – still in use today
(Coughs, colds, parasitic infections, inflammation)
- Vast majority of people on planet still rely on traditional *materia medica*
- WHO estimates ~80%
- Rest also role as 25% prescription drugs are from plants



William Osler

“The desire to take medicines is one feature which distinguishes man, the animal, from his fellow creatures”

Value of phytopharmacology

- Isolate bioactive compounds for direct use as drugs eg. digoxin, morphine, taxol, reserpine
- To produce bioactive compounds of novel or known structures as lead compounds for semisynthesis to produce patentable entities e.g. metformin, oxycodon, verapamil
- To use agents as pharmacologic tools
- To use as a herbal remedy e.g. echinacea, St. John's wort

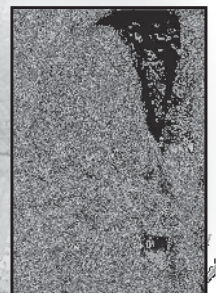
Why we should know about phytopharmacology

- Easily accessible
 - Internet
 - Herbal shops
 - Informal markets
 - OTC
 - Magazines
- Part of our health care system
- Adverse effects occur and we need to treat patients



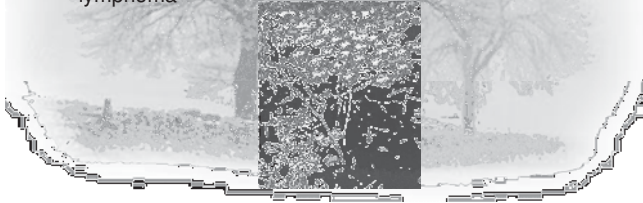
Why used?

- Natural is safe/better
- Desperation
- Culture/beliefs
- Easily accessible
- Economical/Cheaper
- Lack of medical facilities



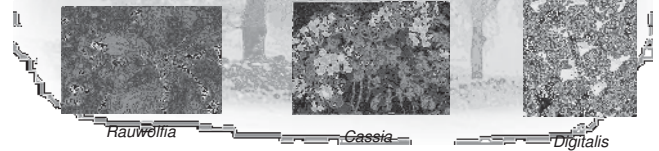
Do plants go out of fashion?

- Bishops weed (*Ammi majus*)
- Egyptians used to treat vitiligo (loss of pigment)
- New drug B-methoxypsoralen
- Uses treat psoriasis, other skin conditions, T-cell lymphoma



Drug discovery: last 40 years

- *Dioscorea* spp. – diogenin: anovulatory contraceptive agents
- *Rauwolfia* spp. – reserpine: anti-hypertensives, tranquilizing alkaloids
- *Pilocarpus* spp. – pilocarpine: glaucoma, dry mouth
- *Cassia* spp. – laxative agents
- *Digitalis* spp. – cardiotonic agent, heart failure



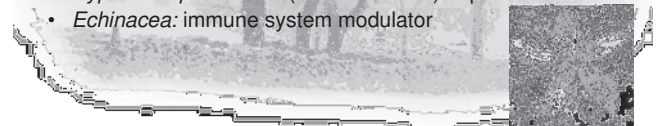
Famous African medicinal plants

- *Acacia senegal* (Gum Arabic): cholesterol, anti-inflammatory
- *Agathosma betulina* (Buchu): prostatitis
- *Aloe ferox/ A. vera* (Cape Aloes): purgative, skin
- *Artemisia afra* (African wormwood): anti-malarial
- *Asplanthus linearis* (Rooibos tea): antioxidant
- *Boswellia sacra* (Frankincense): anti-inflammatory, respiratory, digestive
- *Catha edulis* (Khat): stimulant
- *Commiphora myrrha* (Myrrh): rheumatism, arthritis
- *Harpagophytum procumbens* (Devil's claw): pain, rheumatism
- *Hypoxis hemerocallidea* (African potato): wasting, immune
- *Prunus africana* (African cherry): prostate hyperplasia
- *Catharanthus roseus* (Rosy periwinkle): cancer, diabetes
- *Sutherlandia frutescens* (Cancer bush): immune, wasting



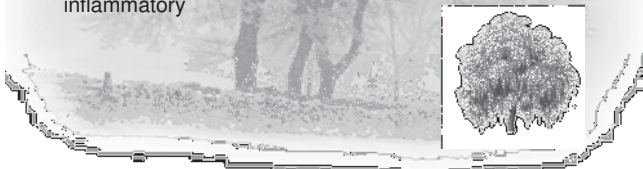
American/Asian/Indian/Chinese

- Chinese > 5000 yr old
- Spread to all continents
- *Panax ginseng*: stimulant, aphrodisiac, DM II
- *Ephedra sinica*: decongestant + bronchodilator (asthma)
- *Ginkgo biloba*: dementia, cerebral deficiencies
- Europe: originated with Hippocrates (460-377 BC)
- Herbal teas
- *Hypericum perforatum* (St John's Wort) depression
- *Echinacea*: immune system modulator



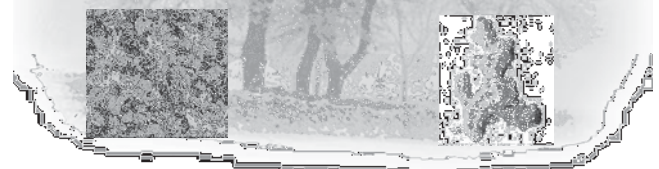
Plants and common uses

- Cocaine from Coca plants: anaesthetics
- *Chondrodendron tomentosum*: alkaloid D-tubocurarine: muscle relaxant in surgery
- *Papaver somniferum*: morphine: analgesic, narcotic
- *Salix* spp.: salicylic acid: aspirin – fever, anti-platelet, anti-inflammatory



Common herbs

- Caraway – bloating
- Coriander – carminative
- Fennel – mildly carminative
- Anis – expectorant, spasmolytic, carminative
- Ginger – travel sickness
- Thyme and mint – broncholytics and expectorants

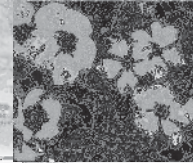


Anti-cancer drugs

- *Catharanthus roseus* (Rosy periwinkle) – vincristine, vinblastine: childhood leukaemia, Hodgkin's disease, breast ca (Velbe: Eli Lilly)
- *Asimina spp* (Papaw) – ovarian ca
- *Taxus brevifolia* (Pacific Yew) -Taxol: ovarian ca (Paclitaxel). Analogs - Docetaxel
- *Podophyllum peltatum* (May Apple) – podophyllotoxin: leukemia, lymphoma, lung, testicular ca (Etoposide/Vepesid)

Anti-cancer

- *Catharanthus roseus* (Madagascar Periwinkle)
- Alkaloids: vincristine + vinblastine
- Inhibit mitosis by binding to tubulin → prevents cell from making spindles
- Side-effects: hair loss, nausea

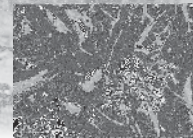


Bronchiodialator

- *Ephedra sinica* (Ephedra)
- Decongestant, bronchiodilator, asthma, hay fever, CNS and cardiac stimulator
- Main component is alkaloid ephedrine, less pseudoephedrine
- Stimulates α_1 , β_1 and β_2 adrenoreceptors
- Ephedrine excites sympathetic NS, causing vasoconstriction + cardiac stimulation
- BP by elevating both systolic and diastolic pressures and pulse rates
- Bad publicity – weight reduction + fat burning products

Diabetes

- *Syzygium cumini* (Java plum)
- Hypoglycaemic effect
- 50% reduction of blood glucose
- ~ 10-fold increase in cathepsin B activity (proteolytic conversion of pro-insulin to insulin)
- Inhibits insulinase activity: liver and kidney



Cardiovascular

- *Rauwolfia serpentina* (Snake-root)
- Alkaloid reserpine
- Hypotensive
- Lowers high blood pressure by depleting tissue stores of catecholamines (epinephrine and norepinephrine) from peripheral sites
- Sedative properties related to the depletion of catecholamines and serotonin from the brain
- Once absorbed from GIT, active alkaloids concentrate in tissues with high lipid content
- Pass BBB and placenta
- Slow onset of action, sustained effect
- CNS and CVS effects persist after withdrawing the drug
- Interacts with/potentiated by some drugs



CNS

- *Hypericum perforatum* (St. John's Wort)
- Nervous disorders
- Hypericin
- Inhibits synaptosomal uptake of neurotransmitters: serotonin, dopamine, noradrenaline and GABA
- Interactions – oral contraceptives, anticonvulsants, cyclosporins, digoxin, HIV protease inhibitors, selective serotonin reuptake inhibitors, etc.



Toxicity

- Plant compounds themselves + part of plant used
- Dosage – overdosage, overduration (seasonal variation)
- Adulteration
- Contamination (Microbial etc.)
- Misidentification/substitution
- Concentrations of compounds not standardized (quality issues)
- Lack clinical trials
- Lack of laws: supplements
- Self-prescription

Adulteration:

- Steroids:
 - prednisolone, hydrocortisone, triamcinolone, methyltestosterone
- Benzodiazepines:
 - diazepam, estazolam, chlordiazepoxide
- Heavy metals:
 - mercury, lead, arsenic, antimony, cadmium
- Analgesics and NSIADs:
 - acetaminophen, aspirin, indomethacin, mefenamic acid
- Other drugs and chemicals:
 - hydrochlorothiazide, digitalis, caffeine, scopolamine, atropine, strychnine, carbamazepine, phenytoin, valproic acid, dipyrrone, diacetyldiphenolisatin

Potential hazards

- Medicinal plants contain mixtures of different chemical compounds:
 - act individually
 - additively
 - synergy
- Modern allopathic – patentable single compound
- Today – used together

Drug-Herb interactions:

- St. John's wort induces cytochrome P450
- Displacement of a strongly protein bound drug by a herb
- Interfering with immunoassays used for measuring [] of a drug in serum/plasma.
- Cyclosporin plasma [], leading to kidney transplant rejection
- Decrease in serum level: oral contraceptives, methadone, warfarin

Pharmacological interference:

- Haematology: increase warfarin's action:(↓ platelet aggregation)
 - Ginseng, Danshen, Garlic, Ginkgo Biloba, Ginger, Devil's Claw, Red Clover, Dong Qui and Horse-Chestnut
- Potassium
 - Licorice ↓ []
- Glucose
 - ↑ Licorice
 - ↓ Garlic, ginger, nettle, sage

Patients presenting with poisonings

- Deny use/think not important to mention (use not disclosed)/not asked
- Herbals exported – not familiar with signs and symptoms
- No information on content
- Area bound
- Acute versus long-term toxic effects
- Direct and indirect indices of toxicity



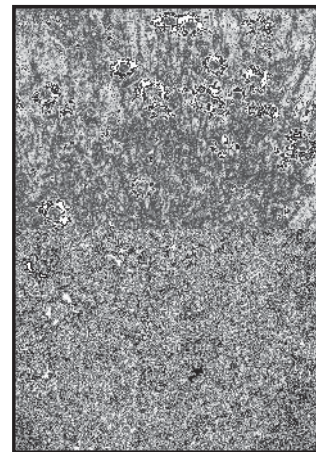
Examples of plant toxicity

Toxin	Species	Effects
Digoxin-like glycosides	Oleander	Cardiac arrhythmias
Hallucinogens	Mushrooms <i>Datura</i> spp.	Delirium
Ricin	Castor oil plant	Haemagglutination
Pyrrolizidines	<i>Senecio</i> spp.	Veno-occlusive liver disease
Solanins	<i>Solanum</i> spp.	Circulatory collapse
Strychnine	Red bitter berry	Convulsions

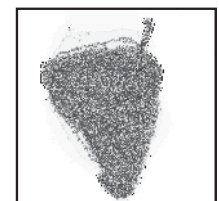
Toxin	Species	Effects
Amphetamine	<i>Catha edulis</i> (Bushman's tea)	Delirium, convulsions
Amanatins	Mushrooms	Hepatic and renal failure
Atractyloside	<i>Callilepis laureola</i>	Mitochondrial toxin
Colchicine	<i>Crocus</i>	Diarrhoea and vomiting Shock, renal failure
Azoglycosides	Cycads	Neurotoxicity, carcinogenesis
Cyanogenic glycosides	Cassava, Apricots	Shock, metabolic failure

Indirect indices of poisoning

- Prothrombin time (coumarins)
- Glucose
- ALT (hepatotoxins)
- Myoglobinuria (myotoxins)
- Haemoglobinuria (haemolytic toxins)
- Methaemoglobin (oxidising agents)
- Hypocalcaemia (+ acidosis)(oxalates)



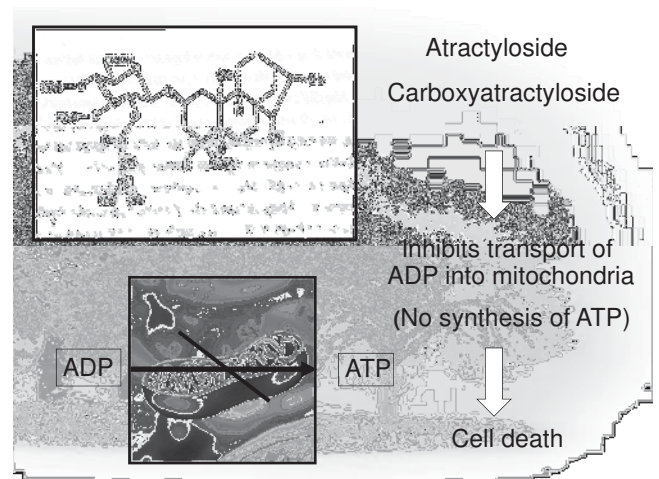
Callilepis laureola DC.
(Ox-eye daisy)
Impila



- Decongestant
- Induce fertility
- Ward off "evil spirits"

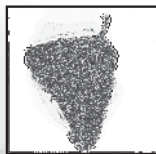
Presentation:

- 80% confused/coma
- 95% hypoglycaemia
- 87% metabolic acidosis
- Hepatocellular failure
- Nephrotoxicity



Treatment:

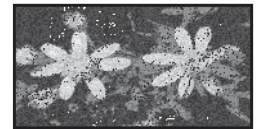
- Supportive
- No antidote



Outcome:

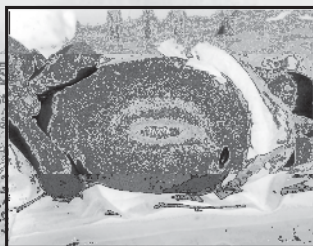
- Survival rates low
- 91% admitted die

Senecio latifolius DC. (Ragwort, groundsel)

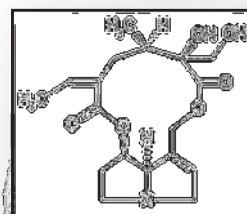


- Induce abortion
- Skin eruptions
- Chest pains
- Palpitations

Presentation



96% ascites
85% hepatomegaly
92% ↑ liver enzymes



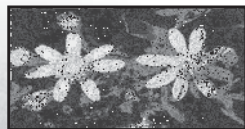
Retrorsine
(pyrrolizidine alkaloid)

Damages vascular
endothelium

VOD

Treatment:

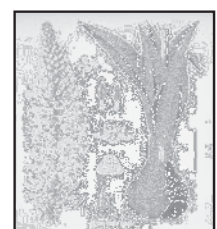
- Supportive
- No antidote
- Counteract thrombosis



Outcome:

- 33% mortality in children < 2 years

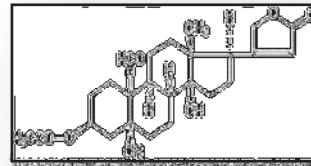
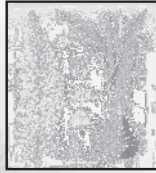
Urginea sanguinea Squill (slangkop)



- Blood purifier
Venereal diseases

Presentation:

- Gastrointestinal symptoms
- Nausea
- Vomiting
- Hyperkalaemia



Scillaren A

Digitalis-like effect

AV block
Rhythm disturbance

Treatment:

- Advanced life support
- Administration of activated charcoal

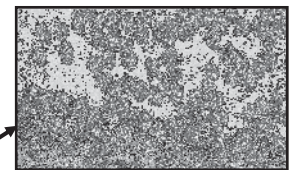
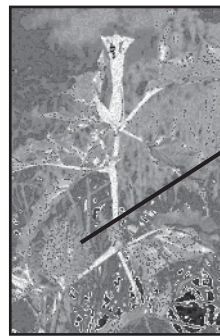
Outcome:

- 57% cases in children < 6 years
- Mortality rare
- Cases due to Oleander poisoning and death



Datura stramonium
(Thorn apple)
(Jimson weed)

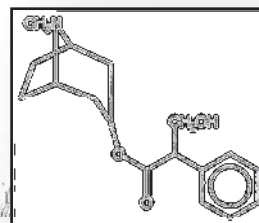
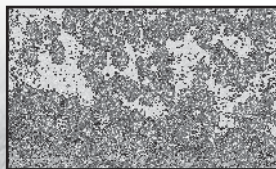
“Malpitte”



T: Asthma
Reduce pain
Headaches
C: Eye drops
Anaesthesia

Presentation:

- Blurred vision
- Suppressed salivation
- Vasodilation
- Delirium



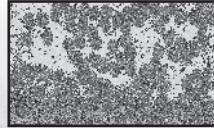
Tropane alkaloids

Atropine
Scopolamine

Anticholinergic activity

Treatment:

- Fluids
- Gastric decontamination: charcoal



Outcome:

- Poisonings sporadic
- No deaths

CLINICAL STUDY

To describe clinical features of patients admitted to hospital with a confirmed history of *muti* ingestion

Patients

- Patients from major teaching hospitals associated with University of the Witwatersrand, Johannesburg
- Requested early urine sample, admission blood tests and clinical data
- 103 patients
 - Total of 127 files reviewed
 - 10 *muti* was suspected but not confirmed
 - 14 data incomplete

Patient data

- Renal function tests available in all patients
- Liver function tests available in 83 patients
- HIV tests available in 64 patients
- Time of use of *muti* prior to presentation available in 28 patients:
 - Median time of use prior to presentation was 4 days (range 0-30 days)
 - 4 patients had repeated use over 7-30 days

Outcome data - demographics

	Survived (n=68)	Died (n=35)
Male (n=64)	44 (68%)	20 (31.3%)
Female (n=39)	24 (61.5%)	15 (38.5%)
Age: <1 year (n=49)	31 (63.3%)	18 (36.7%)
1-2 years (n=3)	3 (100%)	0
2-5 years (n=5)	4 (80%)	1 (20%)
5-15 years (n=3)	2 (66.7%)	1 (33.3%)
> 15 years (n=43)	28 (65.1%)	15 (34.9%)

Organ dysfunction

- Renal dysfunction :
 - 78/103 patients (75.7%)
 - Severe 51/103 (49.5%)
- Liver dysfunction :
 - 40/83 patients (48.2%)
 - Severe 32/83 (38.6%)

Outcome data – organ dysfunction

	Survived	Died
Renal dysfxn (n=78)	46 (59%)	32 (41%)
Severe (n=51, 65.4%)	30 (58.8%)	21 (41.2%)
Without liver dysfxn (n=31)	24 (77.4%)	7 (22.6%)
No renal dysfxn (n=25)	22 (88%)	3 (12%)
Liver dysfxn (n=40)	18 (45%)	22 (55%)
Severe (n=32, 80%)	13 (40.6%)	19 (59.4%)
Without renal dysfxn (n = 8)	6 (75%)	2 (25%)
No liver dysfxn (n = 43)	36 (83.7%)	7 (16.3%)
Renal + Liver dysfxn (n = 32)	12 (37.5%)	20 (62.5%)
No renal/liver dysfxn (n=12)	11 (91.7%)	1 (8.3%)

Time to outcomes

- Time to death available in 31 of 35 patients
 - Median of 3 days (range 1-30)
 - Renal dysfunction: 3.5 days (1-30)
 - Liver dysfunction: 3 days (1-19)
- Time to discharge available in 55 of 68 patients
 - Median of 8 days (range 1-60)
 - Renal dysfunction: 8 days (1-60)
 - Liver dysfunction: 15 (7-52)

Clinical features	Patients	%
Metabolic acidosis	70	72
Dehydration	52	51
Vomiting	47	46
Jaundice/liver failure	41	40
Diarrhoea	40	39
Seizures/encephalopathy	38	37
Respiratory distress/cough	26	25
Kussmaul breathing	26	25
Shock	26	25
Fever	20	19

Most medicinal herbs are reasonably safe for most people most of the time when taken in recommended amounts

Indigenous systems of medicine are dynamic and adaptive, although firmly rooted in the traditions of the past