Asian Indians in Nutrition and Dietetics
Member Interest Group

Asian Indians in Nutrition and Dietetics
a member interest group of the Academy of Nutrition and Dietetics

Berberine

A Bitter Sweet Alkaloid

December 12, 2017

Ellen Kamhi, PhD, RN, AHG, AHN-BC

This webinar will be recorded and available. A copy of the slides and CEU will be emailed to you after the event.

Contact the Academy's membership team at Phone: 312/899-0040 (ext. 5000) or email **membership@eatright.org** to join.

Access the AIND website at http://aind.webauthor.com/.

Community Leader: Parul Kharod MSC RD LDN
Communications Coordinator: Aarti Batavia RDN CLT FSCP IFMCP
Public Policy Leader and Reimbursement Representative: Rita K Batheja MS RDN CDN FAND

Berberine

A Bitter Sweet Alkaloid Story

Asian Indians in Nutrition and Dietetics (AIND) MIG

December 12, 2017

Ellen Kamhi, PhD, RN, AHG, AHN-BC

www.naturalnurse.com

Alkaloids

Berberine

a Bitter Sweet Alkaloid Story

Ellen Kamhi PhD, RN, AHG, AHN-BC

www.naturalnurse.com

Disclosure

- **NaturalNurse.com - President**
  Herbal Certification Courses and CE credits for Nurses, Midwives, Massage Therapists, Nutritionists, RD, Acupuncturists, Private Consultations
- **Natural Alternatives, Inc.- Vice President**
  Radio, TV, Books
- **Consultant Nutraceutical Industry**
  Education, Regulatory, Formulation
- **Ecotoursforcures.com- Vice President**
  Herbal Medicine Making Workshops onground in the US and remote areas of the world, Shamanic Retreats
- **American Herbalists Guild**
  Mentor for Herbalists Pursuing AHG(RH)
- **Stony Brook University- Dept of Family Medicine**
  Clinical Instructor (Botanical Pharmacognocy)
- **Peer Review Editor**
  Alternative Therapies in Health & Medicine, Natural Medicine Journal, Natural Standard (Natural Medicines Database)

Alkaloids

- Alkaloids are organic compounds with at least one nitrogen atom, usually in a heterocyclic ring
- Difficult to define
- Do not represent a homogeneous group on the chemical, biochemical or physiological viewpoint
- Most either sedate or stimulate

Alkaloids

- Alkaloids end in the suffix –INE
- Examples: Caffeine, Ephedrine, Morphine, Berberine, Reserpine, Nicotine, Lobeline etc.
- They are all structurally diverse
- Bitter taste
- Over 10,000 have been identified and many new alkaloids are described daily

Alkaloids

- The name "Alkaloid" refers to the alkaline nature of most of these chemicals, due to the presence of an amino group.
- Most alkaloids are derived from four different amino acids:

Lysine (eg. Sedamine)
Phenylalanine (eg. Ephedrine)
Tyrosine (eg. Mescaline)
Tryptophan (eg. Quinine, Lysergic Acid)

Alkaloids

FUNCTIONS IN PLANTS:

- Poisonous agents that protect the plants against insects, fungus, predators
- End products of nitrogen detoxification
- Regulate growth factors
- Reserve substances which can supply nitrogen when needed

Alkaloids

Distribution:

- Found in animal kingdom in Fire Ants & Toad Venom
- Most occur in annual flowering plants
- Often poisonous but can also be powerful medicine

Alkaloids

http://en.wikipedia.org/wiki/Colorado_River_Toad

Bufo Alvarius

THE PSYCHEDELIC TOAD

Sonoran Desert

http://www.eitangrunwald.com/AZ803/AZ803%20Large/809Bufo_alvarius_DM.jpg

Alkaloids

Bufo Alvarius

Produces 5-MeO-DMT and bufotenin, hallucinogenic tryptamines.

http://www.eitangrunwald.com/AZ803/AZ803%20Large/809Bufo_alvarius_DM.jpg

Alkaloids

ACTIONS:

- Antidepressants
- Respiratory stimulation
- Cardiac stimulants
- Muscle relaxants
- Some are Addictive
- Nervous stimulation
- Nervous suppression
- Analgesia
- Antimicrobial
- Entheogenic
- Mydriatics (atropine)
- Miotics (Physostigmine, Pilocarpine)

Alkaloids

MEDICINAL ALKALOIDS: Examples

- Morphine - analgesic - Opium poppy
- Ephedrine - stimulant- Ephedra, Ma Huang
- Reserpine - relaxant- *Rauwolfia serpentina* (Indian snakeroot)
- Theophylline - bronchial relaxant – *Camellia sinensis* (tea)
- Quinine - anti-malarial agent - Chinchona
- Berberine – antimicrobial - Golden Seal, Barberry

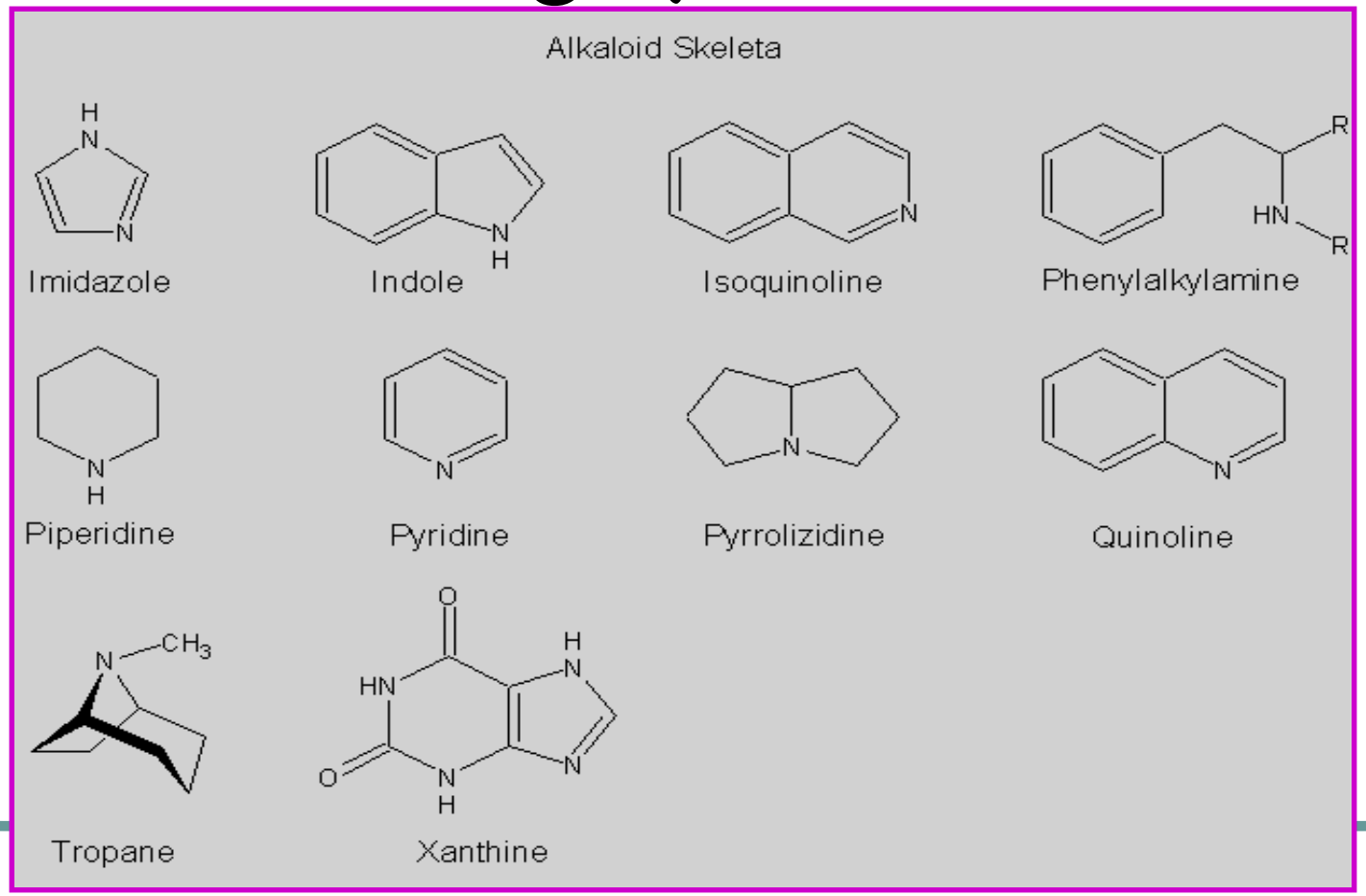
Alkaloids

SAMPLE CATEGORIES:

- Monocyclic
- Bicyclic
- Polycyclic
- Pyrrolidine
- Piperidine
- Tropane
- Purine
- Isoquinoline
- Indole
- Quinoline

Alkaloids

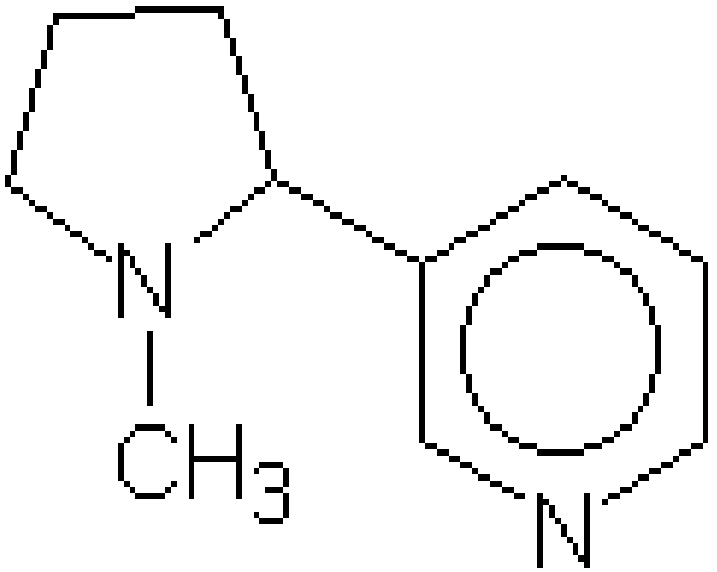
Ring Systems:



Alkaloids

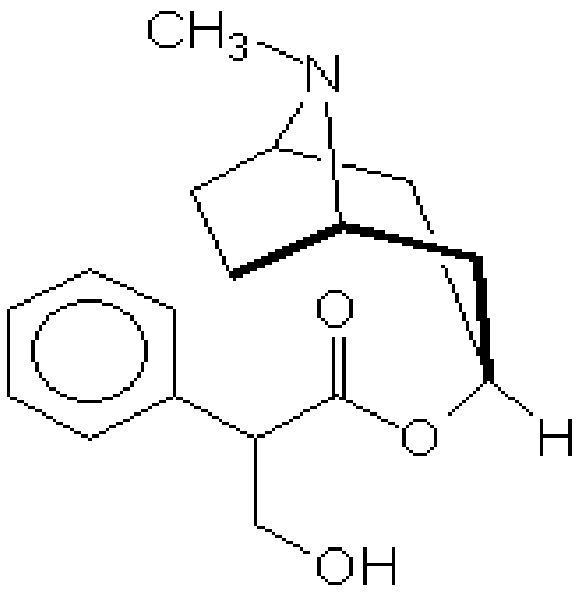
Monocyclic

Contains only one ring



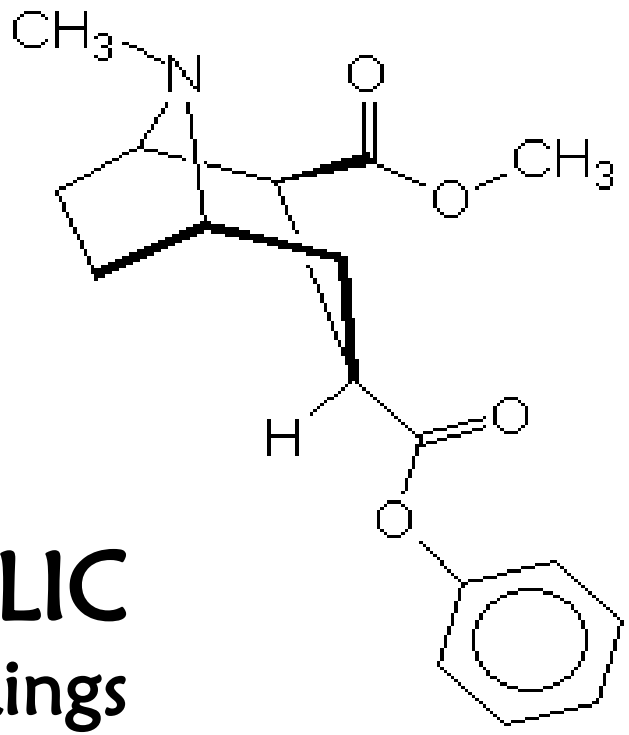
Nicotine

Alkaloids



BICYLIC

Two Rings



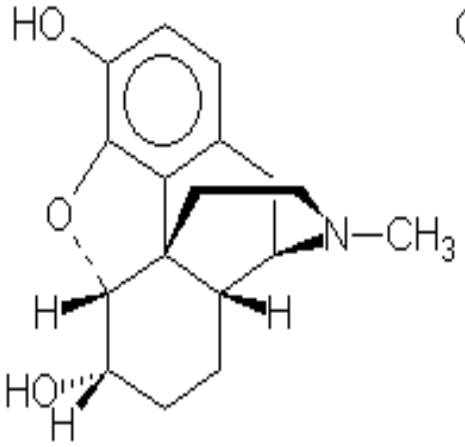
Atropine

Cocaine

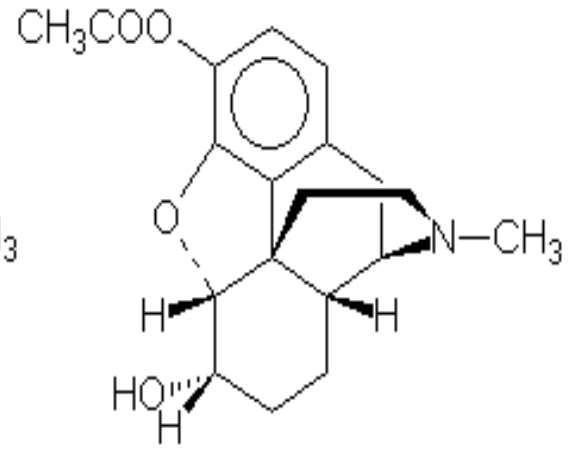
Alkaloids

POLYCYCLIC Many Rings

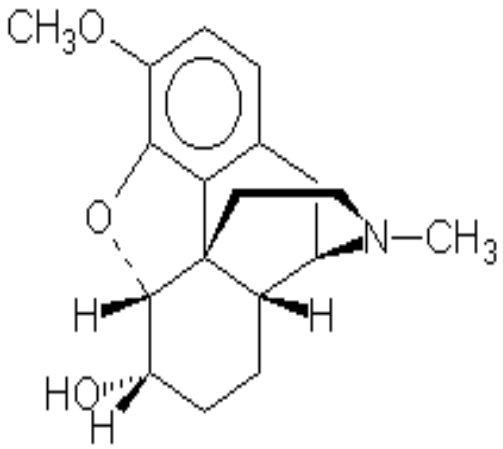
includes strychnine, lysergic acid, cannabinol, morphine, heroin and codeine.



Morphine

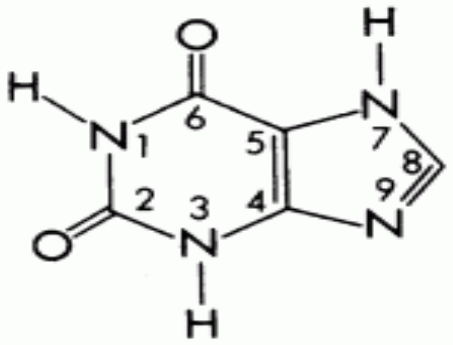


Heroin

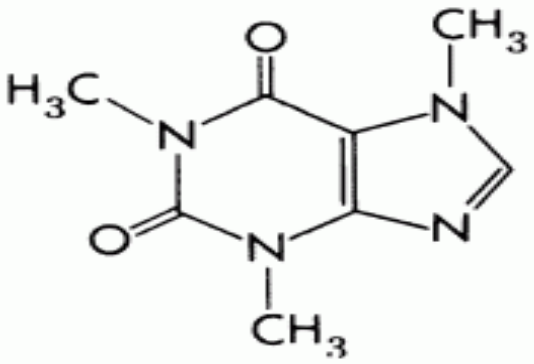


Codeine

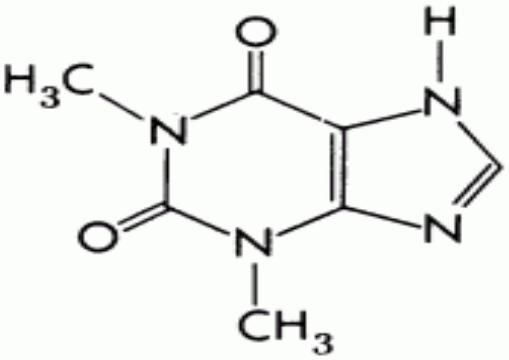
Alkaloids: PURINE



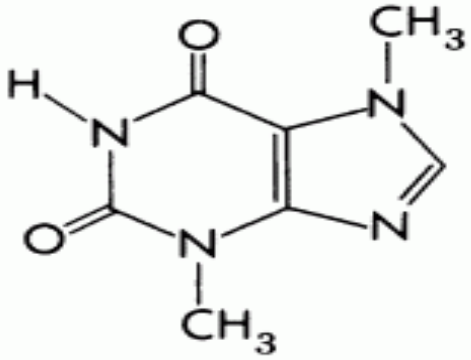
XANTHINE



CAFFEINE



THEOPHYLLINE



THEOBROMINE

http://www.benbest.com/health/xanthines.gif

Alkaloids: PURINE

- CAFFEINE
  coffee, tea, yerba mate
- THEOBROMINE
  cocao
- THEOPHYLLINE
  camellia (Tea), guarana

Alkaloids: PURINE

TEA (*Camellia sinensis)*

- Caffeine is the major methylxanthine
- Theophylline is present in small amounts
- Theophylline used as a drug for asthma & bronchospasm
- 'Side effects' similar to caffeine
- Stimulant, diuretic

LG

Alkaloids: PURINE

- Diuretic
- CNS stimulant
- Anorexia
- Relax bronchospasm
- Enhances NSAID analgesia
- Cardiac & Resp. stimulant

Effects can be surprising: The effects of caffeine on the inducibility of atrial fibrillation. Conclusion: the presence of caffeine may result in an unexpected reduction of AF

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16919674&query_hl=9&itool=pubmed_docsum

Alkaloids: ISOQUINOLONE

California Poppy

Celendine

Blood Root

Golden Seal

Oregon Grape

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Alkaloids: ISOQUINOLONE

Derived from the amino acids Tyrosine and Phenylalanine

Largest group of alkaloids: includes

- Berberine
- Canadine
- Tetrahydropalmatine (THP)
- Morphine
- Sanquinine

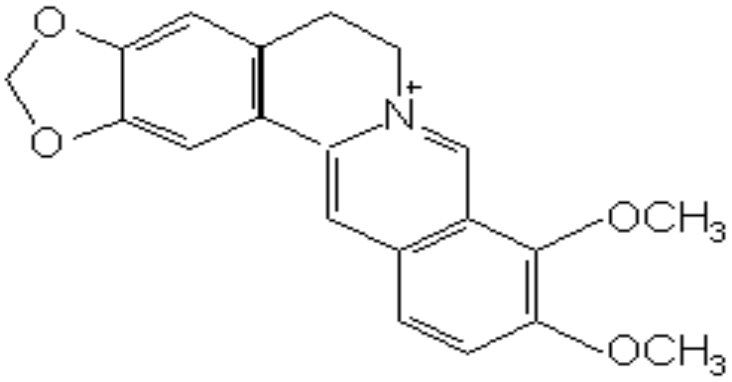
Alkaloids: ISOQUINOLONE

Medicinal Actions:

- Anti-microbial
- Chologogue/choleretic
- Enzyme inhibitor
- Antitumor
- Pain suppressant
- Cough suppressant
- Hypnotic
- Relaxant
- Antispasmodic

Alkaloids: ISOQUINOLONE

BERBERINE



- Yellow in color
- Soluble in ETOH
- Highest concentration in Root bark
- Amoebicidal
- Antibacterial (*Swab on tonsils for strep throat)*
- Anti fungal
- Antitumor
- Bitter
- Hepatic
- Mucus membrane support

Alkaloids: ISOQUINOLONE

BERBERINE

- Found in 23 genera
- Important sources:

Golden Seal
(*Hydrastis canadensis)*

Oregon Grape Root
(*Mahonia Aquafolium)*

Barberry
(Berberis spec)

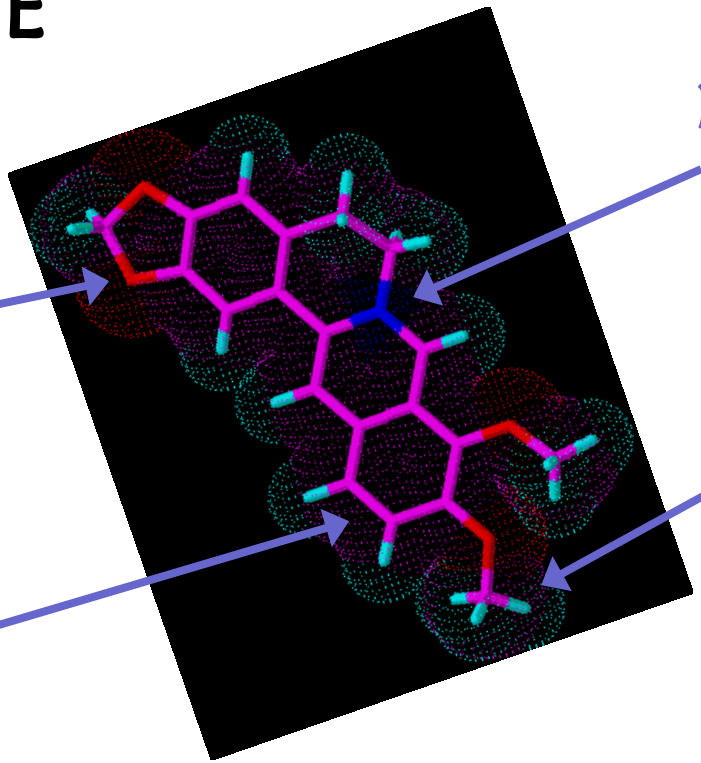
Phellodendron
(Phellodendron amurense)

Bloodroot
(Sanguinaria canadensis)

Chinese Goldenseal
(Coptis chinenesis)

Alkaloids: ISOQUINOLONE

BERBERINE



Nitrogen (blue)

Oxygen (red)

Hydrogen (cyan)

Carbon (magenta)

antimicrobial molecule in Oregon Grape

LG

Alkaloids: ISOQUINOLONE

BERBERINE

Goldenseal & Oregon Grape

- Contain berberine & related alkaloids: antibacterial, antifungal; antibiotic alternative
- Tonic for mucous membranes
- Useful for upper respiratory conditions & UTI's

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Alkaloids: ISOQUINOLONE

Protoberberines: Berberine

- Antiprotozoal (Leishmania)
- Antimicrobial, antiseptic
- Anti-inflammatory, antispasmodic
- Astringent, hemostatic
- Tones mucous membranes
- Bitter digestive tonic

LG

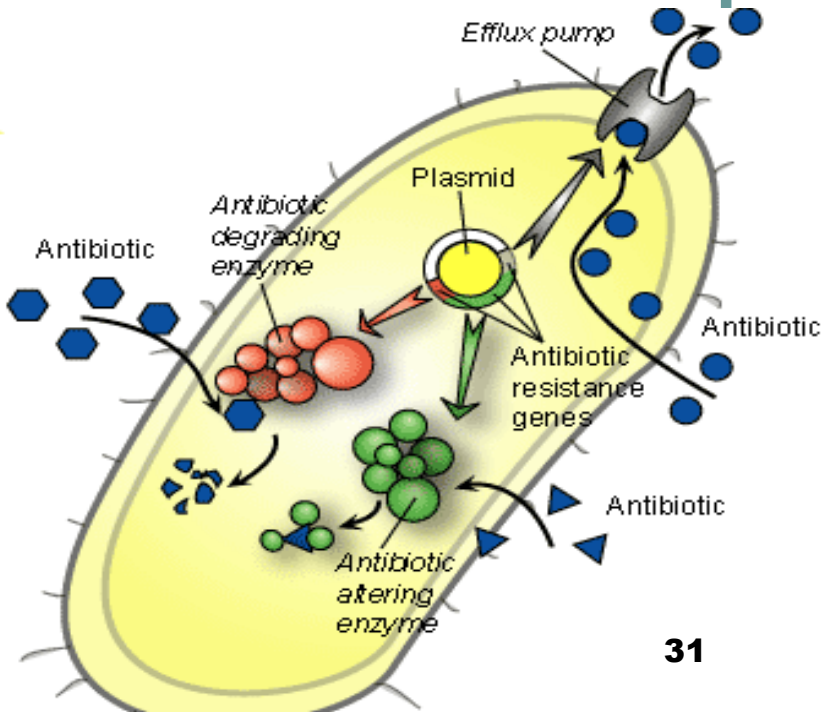
Antibiotics: Use or misuse?

Overuse of antibiotics causes development of resistant strains of bacteria via several mechanisms:

- Chemically modifying the antibiotic
- Rendering the antibiotic inactive through physical removal from the cell

- Modifying the target site so that it is not recognized by the antibiotic

•Inactivating the antibiotic via enzymatic action **(most common strategy)**



Alkaloids: ISOQUINOLONE

BERBERINE

MDR Pump: Multi Drug Resistant Pump
Biological mechanism used by a
cell to rid itself of chemicals

PGP: P-glycoprotein efflux pump

Study on mechanism of action of
5'-MHC-D & pheophorbide-A

http://www.ncbi.nlm.nih.gov/pubmed/12842327

Int J Antimicrob Agents. 2003 Jul;22(1):48-53.

Berberis aetnensis C. Presl. extracts: antimicrobial properties and interaction with ciprofloxacin.

Musumeci R[1], Speciale A, Costanzo R, Annino A, Ragusa S, Rapisarda A, Pappalardo MS, Iauk L.

Author information

Abstract

Previous research showed that berberine-containing Berberis species synthesise the substances 5'-methoxyhydnocarpin-D (5'-MHC-D) and pheophorbide a, which have no antimicrobial activity but inhibit the expression of multidrug resistant efflux pumps (MDRs) in Staphylococcus aureus and potentiate the action of berberine. The MDR pumps extrude synthetic and natural antimicrobials from bacterial cells. We searched for these compounds in Berberis aetnensis C. Presl. (Berberidaceae), an endemic plant of the volcano Mount Etna. This work confirms the presence of pheophorbide a and permits us to hypothesise the presence of 5'-MHC-D in leaf extracts. In fact, the activity of ciprofloxacin was improved when two chromatographic fractions isolated from leaf extracts were added. These results are indicative of the presence of MDR pump inhibitors. Moreover, crude extracts were tested on several micro-organisms and showed antimicrobial activity mainly against Gram-positive bacteria and yeasts.

PMID: 12842327

[PubMed - indexed for MEDLINE]

Sci Rep. 2016 Apr 22;6:24748. doi: 10.1038/srep24748.

Role of Berberine in the Treatment of Methicillin-Resistant Staphylococcus aureus Infections.

Chu M[1,2], Zhang MB[3], Liu YC[3], Kang JR[4], Chu ZY[3], Yin KL[1,2], Ding LY[1,2], Ding R[3], Xiao RX[1], Yin YN[1], Liu XY[1], Wang YD[1,2].

Author information

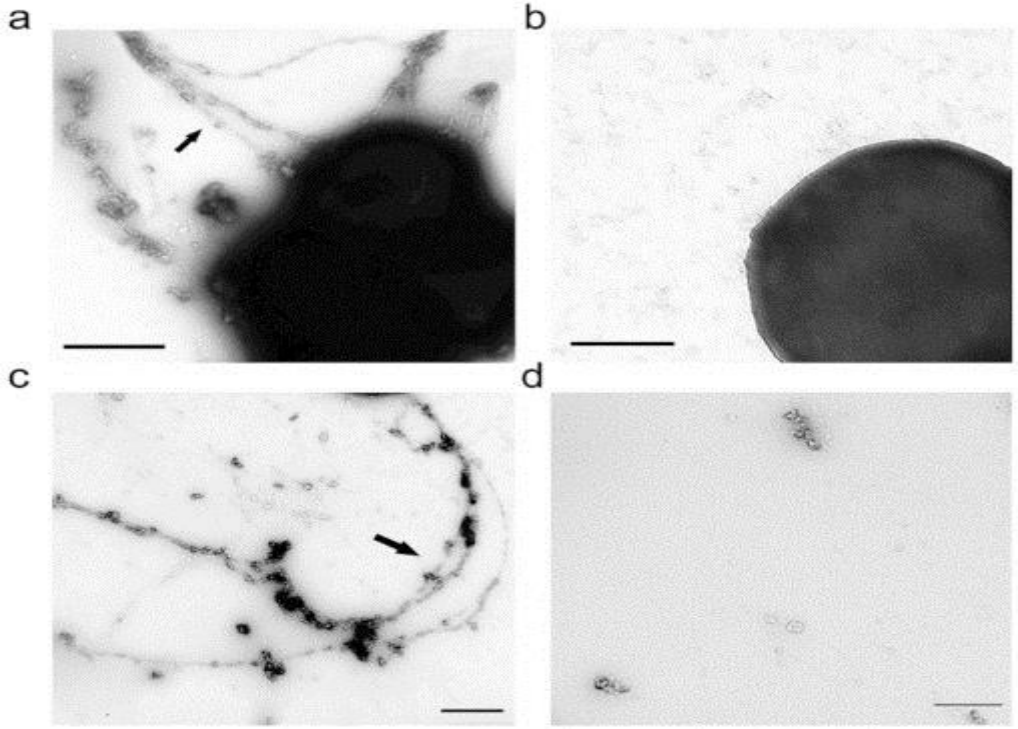
Abstract

Berberine is an isoquinoline alkaloid widely used in the treatment of microbial infections. Recent studies have shown that berberine can enhance the inhibitory efficacy of antibiotics against clinical multi-drug resistant isolates of methicillin-resistant Staphylococcus aureus (MRSA). However, the underlying mechanisms are poorly understood. Here, we demonstrated that sub-minimum inhibitory concentrations (MICs) of berberine exhibited no bactericidal activity against MRSA, but affected MRSA biofilm development in a dose dependent manner within the concentration ranging from 1 to 64 μg/mL. Further study indicated that berberine inhibited MRSA amyloid fibrils formation, which consist of phenol-soluble modulins (PSMs). Molecular dynamics simulation revealed that berberine could bind with the phenyl ring of Phe19 in PSMα2 through hydrophobic interaction. Collectively, berberine can inhibit MRSA biofilm formation via affecting PSMs' aggregation into amyloid fibrils, and thereby enhance bactericidal activity of antibiotics. These findings will provide new insights into the multiple pharmacological properties of berberine in the treatment of microbial-generated amyloid involved diseases.

PMID: 27103062 PMCID: PMC4840435 DOI: 10.1038/srep24748

[PubMed - in process] Free PMC Article

https://www.ncbi.nlm.nih.gov/pubmed/27103062



Inhibitory effect of berberine on MRSA amyloid fibril. micrographs of cells from MRSA biofilms in the culture with berberine

(a) Control

(b) (**b**) 32 μg/mL.

(c) (**c**) 24 hours after mixing 100 μg/mL each of the seven PSM peptides (α1-4, β1-2, and δ-toxin), fibril structures were readily observed by TEM.

(d) (**d**) Few amyloid fibril was observed when PSM peptides were cultured with 32 μg/mL berberine. Bars indicate 500 nm.

Alkaloids: ISOQUINOLONE

BERBERINE

Exophysiological Synergy

- Antibacterial: *Staphylococcus aureus*
- MDR pump (PGP) ejects the berberine
- 5'-MHC-D & pheophorbide-A inhibit PGP
- Berberine stays inside bacteria, kills it

Alkaloids: ISOQUINOLONE

Early Study on Synergy

Synergy in a medicinal plant: Antimicrobial action of berberine potentiated by 5′-methoxyhydnocarpin, a multidrug pump inhibitor

Frank R. Stermitz*, Peter Lorenz*, Jeanne N. Tawara*, Lauren A. Zenewicz†, and Kim Lewis†‡

*Department of Chemistry, Colorado State University, Fort Collins, CO 80523; and †Biotechnology Center, Tufts University, Medford, MA 02155

Communicated by Arnold L. Demain, Massachusetts Institute of Technology, Cambridge, MA, December 13, 1999 (received for review October 6, 1999)

Multidrug resistance pumps (MDRs) protect microbial cells from both synthetic and natural antimicrobials. Amphipathic cations are preferred substrates of MDRs. Berberine alkaloids, which are cationic antimicrobials produced by a variety of plants, are readily extruded by MDRs. Several *Berberis* medicinal plants producing berberine were found also to synthesize an inhibitor of the NorA MDR pump of a human pathogen *Staphylococcus aureus*. The inhibitor was identified as 5′-methoxyhydnocarpin (5′-MHC), previously reported as a minor component of chaulmoogra oil, a traditional therapy for leprosy. 5′-MHC is an amphipathic weak acid and is distinctly different from the cationic substrates of NorA. 5′-MHC had no antimicrobial activity alone but strongly potentiated the action of berberine and other NorA substrates against *S. aureus*. MDR-dependent efflux of ethidium bromide and berberine from *S. aureus* cells was completely inhibited by 5′-MHC. The level of accumulation of berberine in the cells was increased strongly in the presence of 5′-MHC, indicating that this plant compound effectively disabled the bacterial resistance mechanism against the berberine antimicrobial.

bation at 37°C. Growth was assayed with a microtiter plate reader (Bio-Rad) by absorption at 600 nm.

Measurement of Active Transport. Cells were cultured with aeration at 37°C to an OD_{600} of 1.8, pelleted, and washed twice with 20 mM Hepes/NaOH (pH 7.0) buffer. Cells then were resuspended in 1 ml of Hepes buffer at an OD_{600} of 0.3 containing 10 μM CCCP and 10 μg/ml ethidium bromide followed by incubation at 37°C for 30 min (6). The cells were centrifuged, washed, and resuspended at an OD_{600} of 0.15 in Hepes buffer, and fluorescence was measured with a Perkin–Elmer LS-5B luminescence spectrometer at 530-nm excitation and 600-nm emission wavelengths. Measurement of berberine efflux was performed by following a similar procedure with excitation at 355 nm and emission at 517 nm. The concentration of berberine for cell loading was 30 μg/ml.

Isolation of MDR Inhibitors and Structure Determination. Dried, ground leaves (188 g) of *B. fremontii* were submerged in 1,200 ml

LG

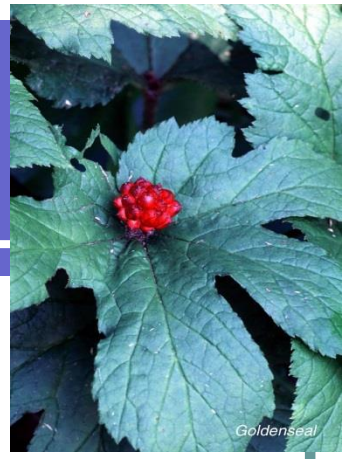
Alkaloids: ISOQUINOLONE

GOLDENSEAL
(*Hydrastis canadensis)*

- Endangered species
- Root most medicinal
- Watch for leaf capsules at lower prices

Hydrastis canadensis L.
Image processed by Thomas Schoepke
www.plant-pictures.de

Alkaloids: ISOQUINOLONE



GOLDENSEAL

Uses: * Soothes Mucous Membranes
* Supports Digestive Processes
* Discourages Microorganisms * Enhances Immune

Function:
* Famous for use against sore throat and Strep throat
* Effective against bladder infections
* Effective against protozoa, bacteria, fungi, including *Candida albicans*
* Eye wash
*Gum rub

Alkaloids: ISOQUINOLONE

GOLDENSEAL

How To Use: Dosage:

- Powdered goldenseal root and rhizome, 4–6 grams per day in tablet or capsule form
- Liquid herbal extracts, 2–4 ml three times per day
- Standardized extracts (8–12% alkaloids) 250–500 mg three times per day

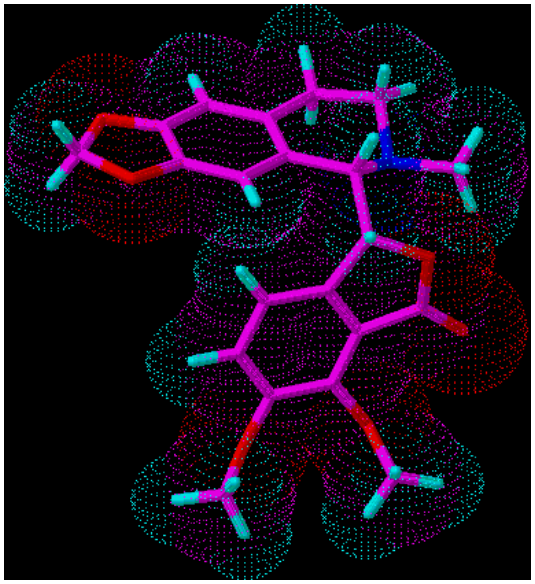
Cautions:

- Continuous use should not exceed three weeks, with a break of at least two weeks between each use.
- gastrointestinal distress
- not recommended for pregnant or breast-feeding women (oxytocic)
- May interfere with tetracycline antibiotics(conflicting studies)
- Goldenseal on endangered species list- replace with Oregon Grape/Barberry

Alkaloids: ISOQUINOLONE

GOLDENSEAL

- Berberine
- Berberastine
- Hydrastine



Hydrastine, a strong antibacterial & fungicide

LG

Alkaloids: ISOQUINOLONE

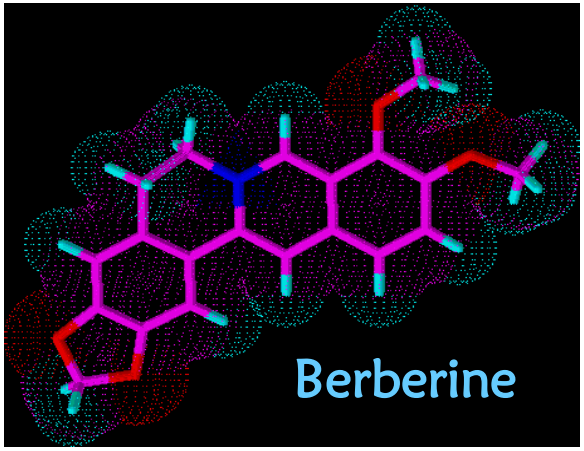
OREGON GRAPE
(*Mahonia aquafolium)*

http://www.chlorischile.cl/cursoonline/guia3/mahonia.jpg

Alkaloids: ISOQUINOLONE

OREGON GRAPE

- Berberine & relatives predominate
- Some hydrastine
- Actions very similar to Goldenseal



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Alkaloids: ISOQUINOLONE

Other Herbs w/Berberine

- Yellow Root (*Xanthorrhiza*)
- Barberry (*Berberis*)
- Goldenthread (*Coptis*)
  contains berberine & coptisine

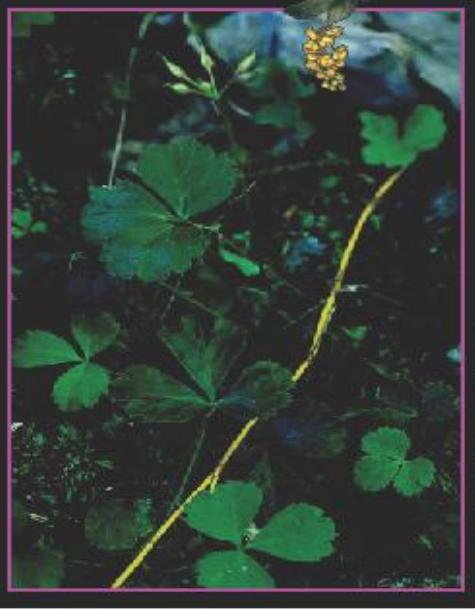

Photo © Martin Wall 2003

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Alkaloids: ISOQUINOLONE

BARBERRY

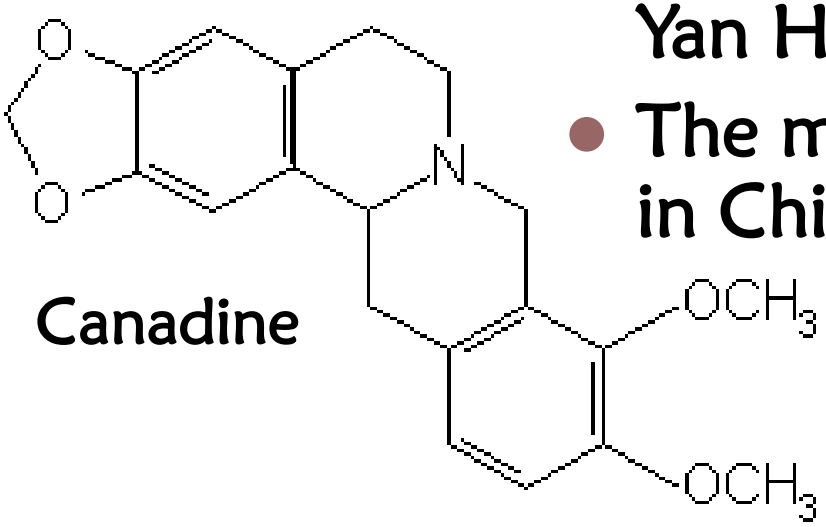
http://en.wikipedia.org/wiki/Image:Berberis_thunb_frt.jpg, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=1806133

Alkaloids: ISOQUINOLONE

CORYDALIS Species
yán hú suo

Alkaloids: ISOQUINOLONE

CORYDALIS Yan Hu Suo



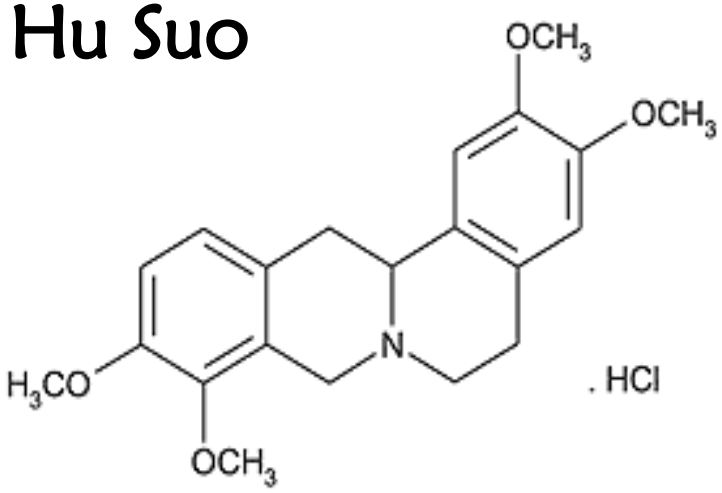
Canadine

- Canadine is found in Corydalis Yan Huo Su
- The most powerful pain killer in Chinese medicine
- Has hypotensive properties

Alkaloids: ISOQUINOLONE

CORYDALIS Yan Hu Suo

- THP found in Corydalis
- 40% as strong as morphine; vinegar extract strongest
- THP is nonaddictive
- Potentiates acupuncture analgesia
- Used in all types of pain in China; one of Nature's most potent pain relievers



Tetrahydropalmatine (THP)

Link: http://en.wikipedia.org/wiki/Tetrahydropalmatine

Alkaloids: ISOQUINOLONE

CORYDALIS Yan Hu Suo

Scientific Studies Support Use :

- Insomnia
- Pain
- Arrhythmia
- **Dysmenorrhea**
- **Stomach Ulcers**
- **Anti-angiogenesis**

J Pharm Biomed Anal. 2017 Mar 20;136:134-139. doi: 10.1016/j.jpba.2017.01.005. Epub 2017 Jan 4.

Screening active compounds from Corydalis yanhusuo by combining high expression VEGF receptor HEK293 cell membrane chromatography with HPLC - ESI - IT - TOF - MSn method.

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Abstract

Corydalis Thizoma,or Yuanhu in China, is a common herbal drug used for thousands of years as analgesic in Chinese medicine that has been reported to have potential anti-angiogenic effects. In this study, a VEGFR/cell membrane chromatography (VEGFR/CMC) coupled with HPLC- ESI-IT-TOF-MSn system was developed and successfully applied for identifying active components from YuanHu extract acting on VEGFR. We identified tetrahydropalmatine and corydaline as bioactive components with VEGFR activity, thus confirming their inhibitory activity on VEGFR engineered HEK293 cell growth by MTT assay. The activity of tetrahydropalmatine and corydaline was compared with the positive control sorafenib in a range of concentration from 6.25 to 50.0μM, showing a dose-dependent inhibitory trend. These results indicate that the VEGFR/CMC coupled with HPLC- ESI-IT-TOF-MSn system can purify and identify specific bioactive components from complex systems, thus representing a promising tool for screening molecules active towards VEGFR from natural herbs.

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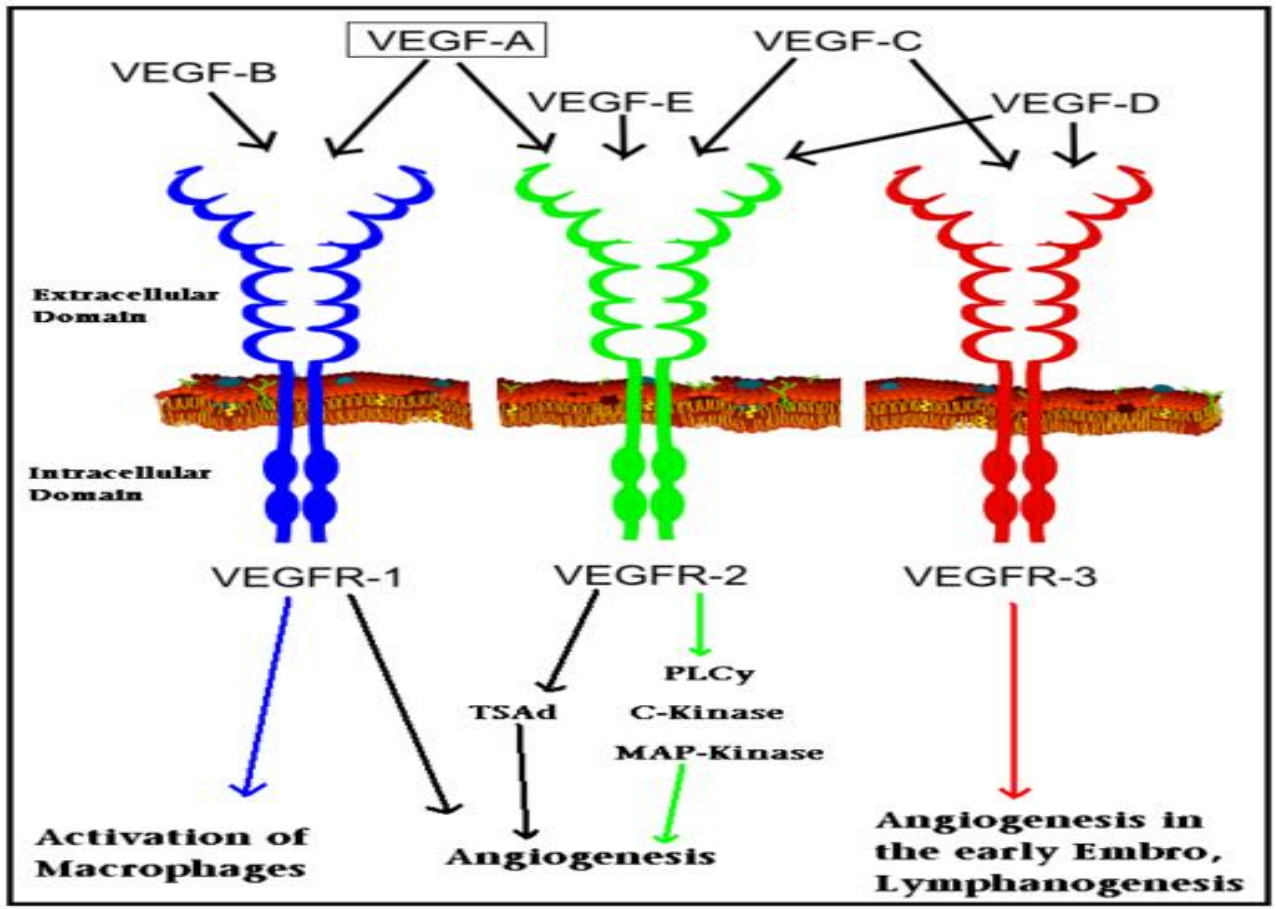
https://www.ncbi.nlm.nih.gov/pubmed/28081499



Vascular Endothelial Growth Factor Receptors (VEGFRs) tyrosine kinase receptors responsible for binding with VEGF to initiate signal cascades that stimulate angiogenesis

Alkaloids: ISOQUINOLONE

CORYDALIS Yan Hu Suo

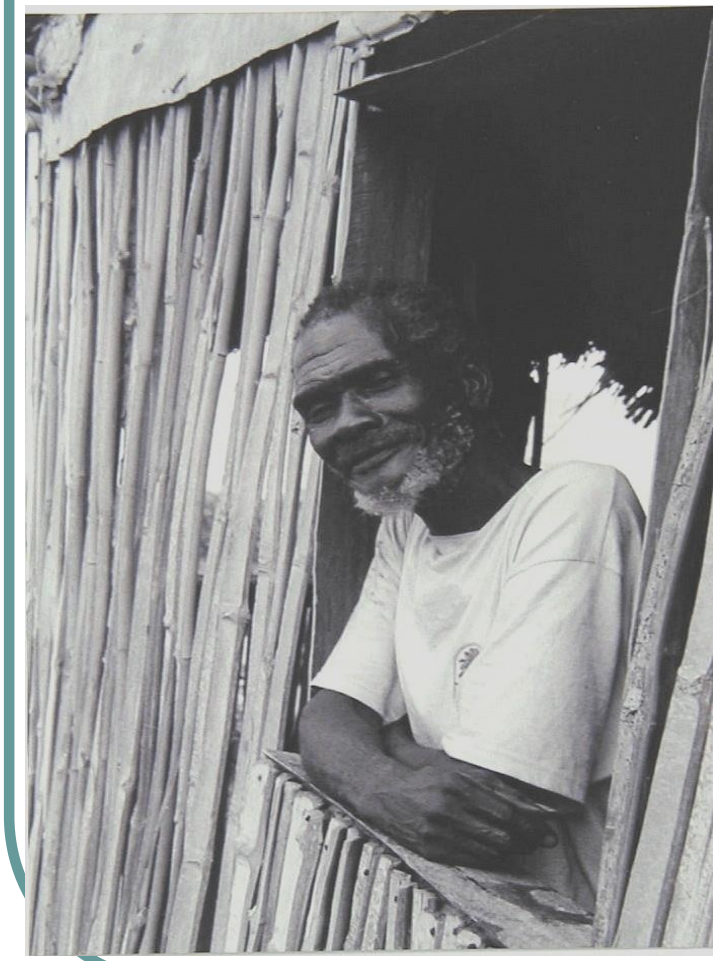
How To Use: Dosage: analgesic or sedative effect

- crude, dried rhizome: 5–10 grams per day/divided doses
- 1:2 fluid extract 10–20 ml per day

Cautions:

- not recommended for pregnant or breast-feeding women
- Reports of THP toxicity/ acute hepatitis
- Possibility of vertigo, fatigue, nausea

JAMBA



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Dr. Diane Robertson, Jamaica's premier natural pharmacist , author & herbalist

TEA

Dr. Kamhi at University of West Indies
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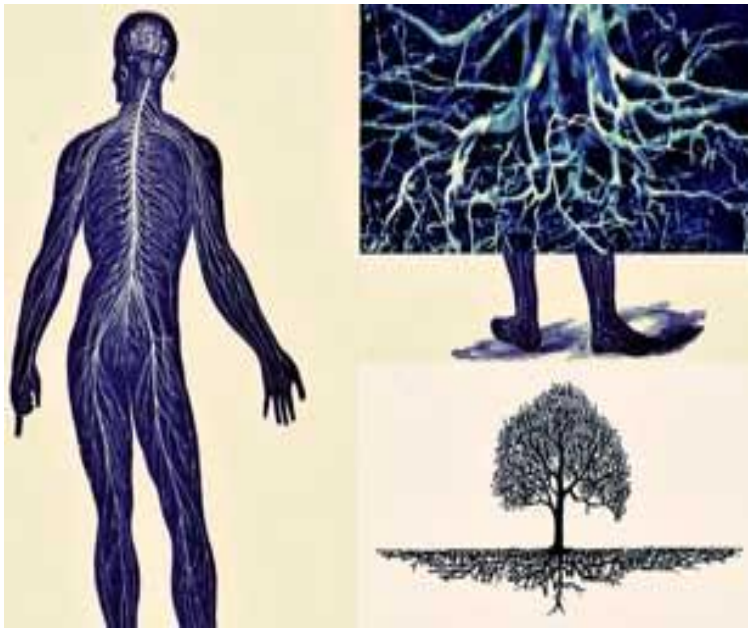

RESOURCES

Ebooks:

Supplements for Pain
Keys to Vitality and Virility
http://www.naturalnurse.com/ebooks/

All Books:
http://www.naturalnurse.com/products/books/

Podcasts- Free
http://www.naturalnurse.com/category/radio-shows/

Additional E-Book Resources through American Association of Physicians of Indian Origin (AAPI):
https://www.aapiusa.org/Resources/Resources

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Thank you!!

Today's speaker Ellen Kamhi w Health Media CEO Alex Lubarsky & Rita Batheja at NAVEL Expo (Nutrition, Aesthetic, Vitality, Efficacy & Life) in Long Island, New York 11/5/17

Pushpa Soundararajan (IL) & Parul Kharod (NC), Developer of Indian Diet - Healthy Plate at FNCE® DPG/MIG Showcase 10/23/2017

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Wahida Karmally, AIND'S Lifetime Achievement Award recipient & Monal Velangi, Professional Advancement for Student Award recipient at DPG/MIG Showcase FNCE® Chicago 10/23/2017

Dr. Varsha, our first contact from Indian Dietetic Association (IDA) India in 1996 honoring Alice Wimpfheimer, Rita Batheja & Esther Myers - AODA president Elect at AODA reception FNCE® Chicago on 10/21/2017

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AIND MIG members at Joint MIG Reception FNCE® Chicago Centennial Celebration 10/23/2017

AIND International members Shilpa Joshi & Monal Velangi from Mumbai India- Wimpfheimer-Guggenheim essay award runners up at AODA reception FNCE® 10/21/2017

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Medallion Award recipients at Member showcase at FNCE® Chicago 10/23/2017

Dietitians In Integrative & Functional Medicine (DIFM) DPG Visionary Award recipient to Rita Batheja at networking reception FNCE® Chicago 10/23/2017

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Asian American Pacific Islanders (AAPI) - AAPI planning meeting - AIND, CADN & FADAN Leadership FNCE® Chicago 10/21/2017

AIND, CADN, FADAN exhibit booth at DPG/MIG Showcase FNCE® Chicago 10/23/2017

Thanks for joining us today!

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Questions?