

**SPECIAL FOREST PRODUCTS CONFERENCE
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**“PLANT DRUGS: WILD CRAFTING FOR
TRADITIONAL USE & BIOEXPLORATION FOR
PHARMACEUTICAL USE”**

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FACTS ABOUT THE USE OF HERBAL PRODUCTS

- 65% of Americans self medicate
 - 33% of Americans pursue some kind of alternative care each year.
 - Herbal supplements are the second fastest-growing category in food and drugstores combined.
 - U.S. sales of natural products in 1994 was \$4 to 7.5 billion.
 - Herbal products are the fastest-growing category of any item sold in pharmacies.
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ECONOMIC SIGNIFICANCE OF PLANT-DERIVED DRUGS

- Over 90% of drugs used in the U.S. prior to 1900 were derived from plants.
 - By 1990, only 25% of prescribed drugs were obtained from plants.
 - Of the 121 clinically useful prescription drugs derived from plants, 74% came to the attention of pharmaceutical companies because of traditional uses.
 - Presently, between 75 to 80% of the world population (mostly in the non-industrialized nations) depend on plant drugs.
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Echinacea

Botanical Source:

Echinacea purpurea L. and other species

Uses: Immunostimulant

Rationale: It increases phagocytosis

Active Principles: Polysaccharides and alkalamides

Goldenseal

Botanical Source: Roots & rhizomes of *Hydrastis canadensis*

Family: Ranunculaceae

Use: Antimicrobial/Astringent

Rationale: Known to inhibit various microbes

Active Principles: Hydrastine & Berberine

Wintergreen

Botanical Source: Leaves of *Gaultheria procumbens*

Family: Ericaceae

Use: Antirheumatic/Antiseptic

Rationale: Salicylates act as anti-inflammatory agents

Active Principles: Methyl salicylate

St. John's Wort

Botanical Source: Hypericum perforatum L.

Family: Clusiaceae

Use: Antidepressant

Rationale: *in vitro*- MAO inhibitor; prevents serotonin reuptake

Active Principle: Unidentified (believed to be a fraction containing xanthenes & flavonoids)

Saw Palmetto (Sabal)

Botanical Source: Serenoa repens Bartr.

Family: Arecaceae

Use: Treatment of benign prostatic hyperplasia

Rationale: Testosterone --> dihydrotestosterone (mediated by 5 alpha - reductase)
Lipoidal extracts of saw palmetto inhibits 5-alpha -reductase activity.

Active Principle: Nonpolar lipophylic fraction

Cranberry

Botanical Source:

Berries of *Vaccinium macrocarphon*

Family: Ericaceae

Use: Urinary tract infection

Rationale: Prevents bacteria from adhering to the urinary tract lining

Active Principle: Unidentified polymeric compound

Bloodroot

Botanical Source:

Rhizomes of *Sanguinaria canadensis*

Family: Papaveraceae

Use: Tinctures - Antiemetic & expectorant
Toothpaste - Prevents dental plaque formation

Rationale: Tincture: Irritant
Toothpaste: Antibacterial & prevents bacterial adhesion

Active Principle: Sanguinarine

Chaparral

Botanical Source: Leaflets of *Larrea tridentata*

Family: Zygophylaceae

Use: Antioxidant & Antinic keratosis

Rationale: Antiproliferative

Active Principle: masoprocol (meso-nordihydroguaiaretic acid)

Capsicum

Botanical Source: Capsicum annum L. var. minimum
Miller and other Capsicum species

Family: Solanaceae

Use: Treatment of intractable pain

Rationale: Substance P is a neurotransmitter which mediates the transmission of pain impulses from the peripheral nerves to the spinal cord. Capsaicin depletes substance P and pain is reduced.

Active Principle: Capsaicin

Cascara

Botanical Source:

Bark of *Rhamnus purshiana*

Family: Rhamnaceae

Use: Laxative

Rationale: Affects the colon

Active Principle: Cascarosides

LEGISLATION WHICH AFFECTED MARKETING OF PLANT DRUGS

- 1938 Food, Drug, and Cosmetic Act.
Required that new drugs be **safe** and **free** from **toxicity**.
- 1962 Kefauver-Harris Amendment.
Required that drugs be **effective** for the use indicated on the labels. Also required that drugs marketed between 1938 and 1962 be tested for their effectiveness.

1962 KEFAUVER-HARRIS AMENDMENT (cont.)

PROBLEMS:

- a. About 5000 prescribed products and 300 ingredients
- b. About 300,000 OTC products and 1000 ingredients
- c. Patents on a natural product?

Pilocarpus

Botanical Source: Leaves of *Pilocarpus jaborandi*
Family: Rutaceae

Use: Glaucoma

Rationale: Cholinergic (ophthalmic) drug

Active Principle: Pilocarpine

Dosage Form: Ocusert

THE USE OF PLANTS TO THE PHARMACEUTICAL INDUSTRY

1. Source of therapeutic agents (e.g., Opium Poppy: morphine and codeine.
2. Source as raw material (precursor) to synthesize useful drugs (e.g., the pill).
3. Compounds found in nature serve as prototypes (models) to synthesize other useful drugs
e.g.: Curare --> synthetic skeletal muscle relaxants
Quinine --> synthetic antimalarials

Curare

Botanical Source: Bark of *Chondodendron tomentosum*

Family: Menispermaceae

Use: Skeletal muscle relaxant

Rationale: Nicotinic receptors at the neuromuscular junction are blocked

Active principle: Tubocurarine

Prototype: For synthetic skeletal muscle relaxants

Cinchona

Botanical Source: Bark of *Cinchona succirubra*

Family: Rubiaceae

Use: Malaria & Cardiac arrhythmias

Rationale: Quinine-Antiprotozoan
Quinidine-Cardiac arrhythmias

Active Principle: Quinine & quinidine

Prototype: Synthetic antimalarial (e.g., chloroquine)

Bioprospecting Strategies

1. Random search
 2. Ethnobotanical search
 3. Ecologically/Taxonomically informed search
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Pacific Yew

Botanical Source: Bark of *Taxus brevifolia*

Family: Taxaceae

Use: Ovarian & breast cancer & Kaposi's sarcoma

Rationale: Antimitotic agent

Active Principle: Paclitaxel (Taxol)

Prototype: For docetaxel (Taxotere)

Coca

Botanical Source: Leaves of *Erythroxylum coca*

Family: Erythroxylaceae

Use: Local anesthetic

Rationale: Blocks generation and conduction of nerve impulses

Active principle: Cocaine

Prototype: Synthetic local anesthetics (e.g., procaine)

Mayapple

Botanical Source: Roots & rhizomes of *Podophyllum peltatum*

Family: Berberidaceae

Use: Topical - Removal of venereal warts
Systemic - Treatment of cancer

Rationale: Antimitotic agent

Active Principle: Podophyllotoxin

Prototype: Semisynthetic derivatives:
Etoposide - testicular cancer
Teniposide - lymphoblastic leukemia

Cacao

Botanical Source: The roasted seeds of *Theobroma cacao*

Family: Sterculiaceae

Use: Improves coronary blood flow

Rationale: Dilates coronary vessels

Active principle: Theobromine

Prototype: For pentoxifylline (Trental) used in intermittent claudication

TAXOL

Taxus brevifolia (Pacific Yew)

Taxus baccata (European Yew)

Nonrenewable Resource:

We require bark from 3-7 (200 year old) Pacific Yew trees to produce 2.0--2.5 grams of taxol to treat one patient with ovarian cancer.

Approximately 100,000 trees are needed per year to treat patients with ovarian cancer alone.

Approximately 3,000 trees (9,000 Kg of bark) produce 1 Kg. of taxol.

ADVANTAGES IN USING PLANT CELL CULTURES
FOR THE PRODUCTION OF NATURAL
SUBSTANCES (SECONDARY METABOLITES)

1. Independence from various environmental factors (i.e., climate, pests, geographical, and seasonal constrains).
2. Control over production (i.e., production as & when required and the amount required depending on the market demands).
3. Preservation of natural forests and wild species.
4. Reduction in land use.

ADVANTAGES IN USING PLANT CELL CULTURES
CONT:

5. Freedom from political interference.
6. Consistent quality and yield.
7. Production of new compounds (i.e., Vomilenine, a new alkaloid from *Rauwolfia* cells).
8. Products from plants difficult to grow and from plants harvested after several years of growth (i.e., Sandalwood).
9. Biotransformation.

INDUSTRIAL APPLICATION OF
PLANT TISSUE CULTURES

<u>Product</u>	<u>Species</u>	<u>Company</u>	<u>Country</u>
Shikonin	<i>Lithospermum Erythrorhizon</i>	Mitsui	Japan
Berberine	<i>Coptis Japonica</i>	Mitsui	Japan
Digoxin	<i>Digitalis lanata</i>	Boehringer Mannheim	Germany
Taxol	<i>Taxus brevifolia</i>	Phyton Catalytic	U.S.
Vinca Alkaloids	<i>Catharathus roseus</i>	?	Germany & U.S.

Taxol From Fungi

Source:
Taxomyces andreaeae
Pestalotiopsis species
Monochaetia species
Alternaria species

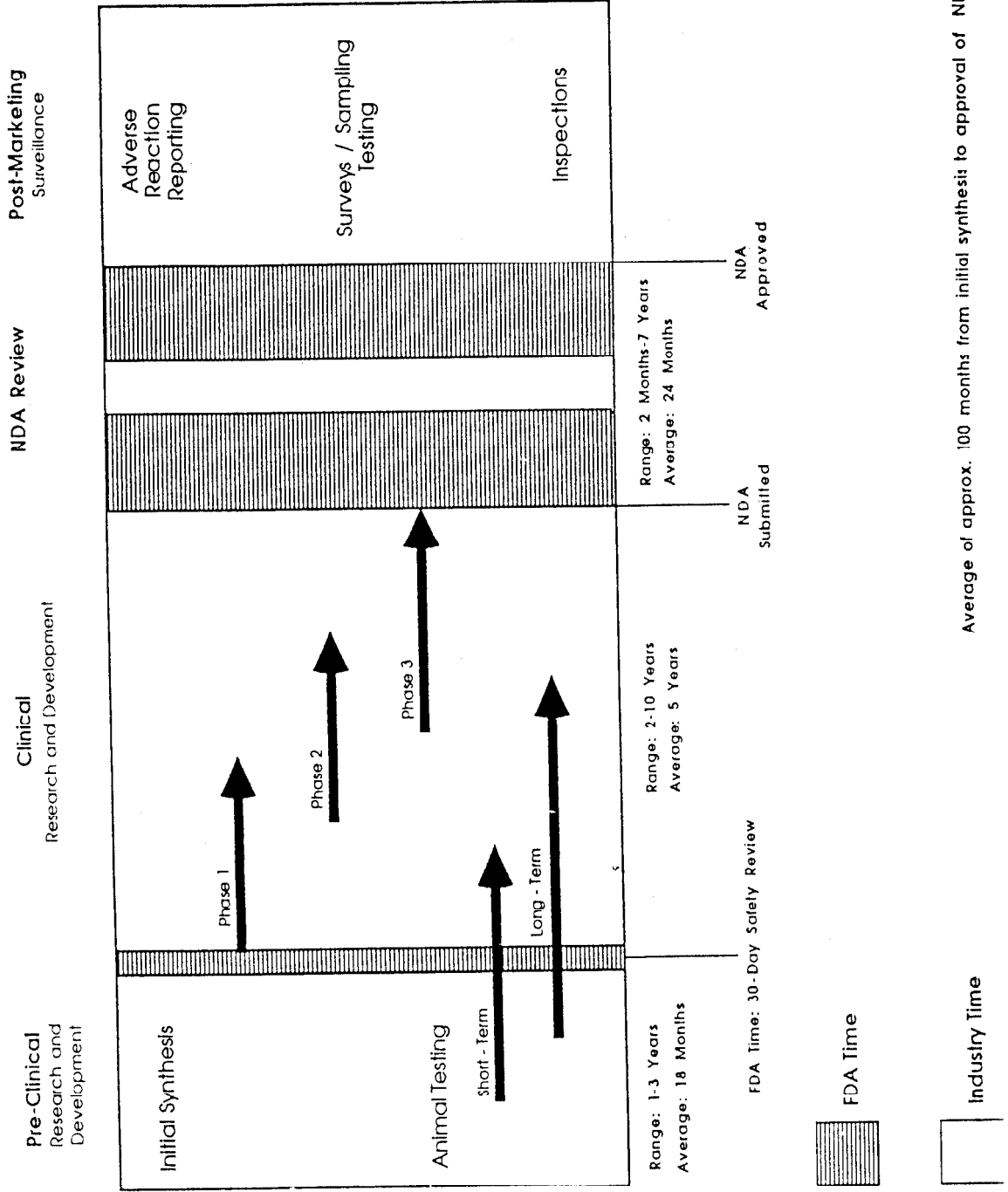
Pau de arco

Botanical Source:
 Bark of *Tabebuia* species
Family: Bignoniaceae
Use: Antioxidant, antitumor & antibiotic
Rationale: Antimitotic agent
Active Principle: Lopachol (naphthoquinone)
Prototype: Semisynthetic derivative
 3-allyl-B-lapachone
 Clinical Trails in Progress in Brazil

Birch

Botanical Source: Bark of *Betula* species
Family: Betulaceae
Use: Treatment of melanoma
Rationale: Antimitotic agent
Active Principle: Betulin/Betulinic acid
 Clinical trials in progress in the U.S.

New Drug Development



TITLE	AUTHOR/TITLE	AVAILABILITY
American Herbal Pharmacopoeia (AHP)	Upton, R, ed.	AHP, Box 5159, Sanla Cruz, CA 95063, phone (408) 461-6317
Handbook of Medicinal Herbs	Duke, JA	Boca Raton, Florida: CRC Press; 1985
German Commission E Monographs	Blumenthal, Gruenwald, Hall, Riggins, Rister, ed., Klein & Rister (trans) (in press)	American Botanical Council, P.O. Box 201660, Austin, Texas 78720, phone (512) 331-8868 fax (512) 331-1924
HerbalGram Journal of the American Botanical Council and the Herb Research Foundation	Blumenthal M, ed	American Botanical Council, P.O. Box 201660, Austin, Texas 78720, phone (512) 331-8868, fax (512) 331-1924.
Herbal Medicines: A Guide for Health-Care Professional	Newall C, Anderson L, Phillipson J	London, UK: The Pharmaceutical Press, 1996
Herbs of Choice: The Therapeutic Use of Phytomedicinals	VE Tyler	Binghamton, New York: Phamaceutical Products Press (Haworth Press); 1994.
Herbal Drugs and Phytopharmaceuticals	Bisset NG, ed.	Boca Raton, Florida: CRC Press; 1994.
The Honest Herbal, 3rd Edition	VE Tyler	Binghamton, New York: Phamaceutical Products Press (Haworth Press); 1993.
Lawrence Review of Natural Products	Loin, BR, ed.	St. Louis, Missouri: Facts and Comparisons; 1997.
Rational Phytotherapy	Schulz V, Hansel R, Tyler VE	Springer, Berlin, 1997.