



Further Development of Herbal Medicines as New Drugs

- A Pharmacognosist's Perspective*

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*Personal views may not represent those of the presenter's current and previous employers

Outlines

- What is pharmacognosy?
 - Botanical Drug Guidance and review of botanical INDs
- Brief introduction to Chinese Herbal Medicines
- Purified Prescription drugs from medicinal plants
 - Well-known examples: Artemisinin and Paclitaxel
- OTC and prescription botanical drugs from medicinal plants
 - Examples of OTC monographs
 - Final (GRASE, Category I): Witch Hazel and Pyrethrins)
 - Not Final (Category III): Senna, Psyllium
 - Recently approved botanical drugs (NDAs)
 - Veregen (Sinecatechins) for genital warts
 - Fulyzaq (Crofelemer) for HIV related diarrhea
- Discussions and closing remarks

Education and Professional Background

- **Beijing University of Chinese Medicine (1980-1991)**
 - BS (Pharmacy, 1984); MS (Pharmacognosy, 1987)
 - Teaching Assistant and Lecturer in Pharmacognosy (08/1987-07/1991)
- **University of Mississippi (1991-1995)**
 - PhD. in Pharmacognosy (Mentor: Distinguished Professor James McChesney)
- **University of Kansas (1996)**
- **NaPro Biotherapeutics (12/1996-07/2002)**
 - Scientist, Manager of Process development of EIP process of paclitaxel from yew twigs
 - Analytical and process development, and manufacturing of paclitaxel API
 - New anticancer drug discovery and development
- **FDA as Pharmacologist/Pharmacognosist (07.2002-present)**
 - Currently expert reviewer in OPS, CDER
 - Participated in a FDA working group for developing the final rule on ephedrine-containing dietary supplement

What is Pharmacognosy?

- ASP-American Society of Pharmacognosy (Established in 1959)
 - <http://www.phcog.org/>
- Pharmacognosy is the study of medicines derived from natural sources
 - ASP defines pharmacognosy as "the study of the physical, chemical, biochemical and biological properties of drugs, drug substances or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources"
 - In other words, pharmacognosy involves multiple disciplinary study (e.g., previous human experience, biology, chemistry, pharmacology) of natural products for the purposes of new drug discovery and development

FDA's Botanical Drug Guidance*

Guidance for Industry Botanical Drug Products

Copies of this Guidance are available from:

*Division of Drug Information (HFD-240),
Office of Training and Communications,
Center for Drug Evaluation and Research (CDER),
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573*

Internet at <http://www.fda.gov/cder/guidance/index.htm>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2004

Final guidance published on
06/09/2004

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf>

Other CDER guidance*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

* Under revision

Pharmacognosy Review of Botanical Drugs

- Medicinal plant biology
 - Identification, potential misuse
- Pharmacology of botanical drugs
 - Old theories and new testing
- Prior human experiences
 - Mostly in complementary and alternative medicine (CAM), systems such as TCM
- More
 - Ensuring quality and therapeutic consistency

Botanical Review Team

- CDER/OND/ODE-V (2002-2004)
 - Dir., Jonca Bull
 - Team members, Shaw Chen (TL), Jinhui Dou (reviewer) and a PM
- CDER/OND/ODE-I (2005-2008)
 - Dir., Bob Temple
- CDER/OND/ODE-IV (2009-02/2014)
 - Dir., Charles Ganley/Acting Dir., Sandy Kweder
- CDER/Office of Pharmaceutical Science (03/2014-present)
 - Dir., Lawrence Yu
 - Team Leader (Associate Dir. of OPS), Sau (Larry) Lee
 - Reviewers: Jinhui Dou and Charles Wu

Botanical Applications in CDER, FDA (as of December 31, 2012)

- Total of 550 pre-INDs/INDs
 - 430 INDs (2/3 active); 120 pre-INDs
 - 53 in 1990-'98, 497 in 1999-2012, ~3-4 per month
- Approx. 1/3 commercial, 2/3 research
- 2/3 single herb, 1/3 multiple herbs
- Mostly phase 2, and a few in Phase 3
- Two NDAs submitted and approved

* In 2013, approximately 60 new pre-IND/IND submitted.



Chinese Herbal Medicines



Traditional Chinese Medicine (TCM)

- TCM is a medical system that the Chinese people have developed throughout the long history of Chinese civilization and used to ward off diseases, protect and promote human health
 - Yin-Yang is at the heart of TCM theory
 - Yin-Yang is used to characterize all the matters in the world
 - Human life and natural environment should be harmonized
 - **Yin-yang balance is the foundation for good health**
 - Food and medicine all originated from nature
 - Green tea 茶 and alcoholic beverages 酒 have medicinal values
 - 是药三分毒 “Herbal medicines may have certain degrees of toxic or adverse effects”

Prominent TCM Classics and Doctors (1 of 3)

- ***Yellow Emperor's Inner Canon***
《黄帝内经》 (ca. 476-221 BC)
 - A must-read classic for today's TCM physicians
- ***Shennong Emperor's Classic of Materia Medica***
《神农本草经》 (ca. 100-200 AD?)
 - First herbology classic, recorded 365 herbs
 - (252 plant parts, 67 animal parts, 46 minerals)
- ***Prescriptions for Fifty-two Diseases***
《五十二病方》 (ca. 202 BC to 9 AD)
 - Unearthed in 1973

Prominent TCM Classics and Doctors (2 of 3)

- **Hua Tuo** (ca. 140–208 , top right picture)
 - The divine doctor 神医
 - "Exercise of the Five Animals" tiger, deer, bear, ape, and crane 五禽戲
 - Invented an herbal anesthesia for surgery (麻沸散)
- **Zhang Zhongjing** (ca. 150—219, middle right picture)
 - 张仲景, Sage of Chinese Medicine 医圣
 - *Treatise on Cold Pathogenic and Miscellaneous Diseases*, formulas are still used in China and Japan
《伤寒杂病论》
- **Sun Simiao** (ca. 581 or 540–682, bottom right picture)
 - 孙思邈, China's King of Herbs 药王
 - *Essential Formulas for Emergencies of a Thousand Gold*
《千金要方》
- **Su Jing** 苏敬 et al. (Ed. 657-659) Newly Revised *Materia Medica*
 - The first government published pharmacopeia
《唐-新修本草》



Prominent TCM Classics and Doctors (3 of 3)

- Zhu Xiao (朱櫨, 1360-1425) 《救荒本草》
Herbs as Food Substitute for Survival (1406)
 - Ming Dynasty 1st Emperor's 5th son
 - 414 herbs with 276 first recorded by Zhu
 - Chinese Toon 香椿, *Toona sinensis*, is now enjoyed by both Chinese and Americans
- Li Shizhen (李时珍, 1518 – 1593, pictured)
《本草纲目》 **Compendium of Materia Medica**
 - Took 27 years to complete
 - The book contains 1894 herbs with 1109 drawings (e.g., *Ginkgo biloba*), and over 11,000 formulas
 - 1st published in 1596
 - Translated into several other languages



TCM as an Evolving and Advancing System

- TCM has influenced the traditional medicine systems of other countries
 - E.g., Korea, Japan, and other Southeastern Asian countries
- Significant number of TCM herbs were introduced from overseas
 - Li Xun 李珣 (907-960) *Herbs from Overseas* 《海药本草》
- Contributions to modern day new drug development
 - Artemisinin (qinghaosu 青蒿素) developed from a TCM herb *Artemisia annua* in the 1970s
 - Professor Tu Youyou 屠呦呦 won the prestigious Lasker Award in 2011 for her contribution
 - Ge Hong's (ca 284-364) “Formulas for emergency” 《肘后方》 recorded Qin Hao for treating malaria

Integration of TCM and Western Medicine

- Integrated Western medicine and TCM system in China
 - Chinese Pharmacopoeia (Vol 1 Chinese Herbs and Plant Derived Drugs)
 - TCM doctors also trained in Western Medicine and vice versa
- Chinese government support further R&D of TCM
 - MOST (Ministry of Science and Technology) and MOH
 - Natural Science Foundations
- High expectations and challenging issues
 - Searching for new drugs (botanical or purified) from TCM and other herbal medicines
 - TCM products widely used for hepatitis, flu and SARS
 - More R&D including well-designed clinical trials needed to confirm efficacy and safety to convince western scientists and regulators (e.g., US FDA)
- US NIH (ODS and NCCAM) support TCM research as “dietary supplements” and “complementary alternatively medicines”
 - Challenges of ensuring safety for herbal medicines as “dietary supplements”
 - CAM and new drug development overlap

TCM as Complementary and Alternative Medicine in the West

- US- Many herbal supplements are imported from China (TCM)
 - Part of Asian American (especially Chinese American) culture
 - The Chinese railroad workers used TCM for routine medical needs since the early 1850s (CPRR)
 - A TCM doctor, Yee Fung Cheung, used an Ephedra formula to “save the life” of Jane Stanford, wife of CA Governor and CPRR President
- Canada-Natural health products
 - Drug claims based on traditional use permitted
- EU-Herbal medicines



FDA Regulate Products Derived from Plants



Categories of FDA Regulated Products

- Food
 - Food with health claims
- Dietary supplements (herbs/botanicals)
 - Structure/function claims
 - Herbs (or Herbal Medicines)
 - Not regulated as “drugs” in the United States
- Drug products:
 - Non-prescription (OTC) or prescription drugs
- Other (e.g., cosmetics, devices)

Ephedra: TCM Herb, Mormon Tea, or Drug?

- Ephedra has been used for coughing and asthma in TCM for over 2000 years
 - For short term cold/cough symptom relieve for certain patients at moderate doses
 - Cases of heart failure, death (大汗亡阳) recorded in TCM classics
 - TCM theory and doctors advise patients not taking ephedra if patient sweats (or having other contradictions)
- Ephedra species
 - Chinese Pharmacopeia listed *E. sinica*, *E. intermedia*, *E. macropholia*
 - Chinese Ephedra contain ephedrine and pseudoephedrine at more than 1%
 - US species (e.g. *Ephedra nevadensis* and *Ephedra viridis*) used in Mormon Tea do not contain ephedrine (alkaloids)



Ephedrine Alkaloids Not Safe as Dietary Supplements

- Dietary supplements containing ephedrine caused serious AEs and deaths in late 1990s and early 2000s
 - Used for sports enhancement and weight control by the general populations, including athletes
 - Steve Bechler, a pitcher for the Baltimore Orioles, died of complications from heatstroke following a spring training workout on February 17, 2003.
 - Ephedra (ephedrine alkaloid) toxicity played a "significant role"
 - Toxicity related to dose and duration
 - In some extreme cases, consumers of dietary supplements used ephedrine at multiple gram quantity for weeks/months
- Federal Register: February 11, 2004 (Volume 69, Number 28)

Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk

Methamphetamine-An derivative from Ephedrine Related Alkaloids

- Methamphetamine (or N-methyl-alpha-methylphenethylamine) is a neurotoxin and potent psychostimulant
 - Approved to treat attention deficit hyperactivity disorder (ADHD) and obesity
 - With black box warning
 - Class II controlled substance
 - Abused substance with a street name “meth” and often made illegally in “kitchen/meth labs”
- Methamphetamine can be made from ephedrine through simple chemical reactions



Ephedrine Alkaloids as Drugs

- Ephedrine (plant derived or synthetic)
 - One old drug for treating asthma
 - Used as a stimulant by Japanese pilots during World War II
- Pseudoephedrine, an ephedrine-like molecule in certain Ephedra species, used in OTC monographs
 - An active ingredient in over three dozen allergy/cold medicines, such as ADVIL COLD AND SINUS, ALEVE-D SINUS & COLD, CLARITIN-D (and 24 hour), and ZYRTEC-D 12 HOUR, etc.



“Plants that Heal”- Plant Derived Drug Products

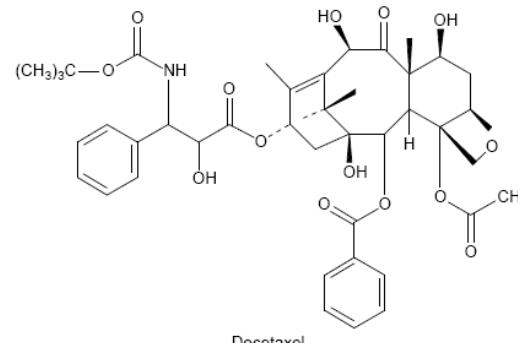
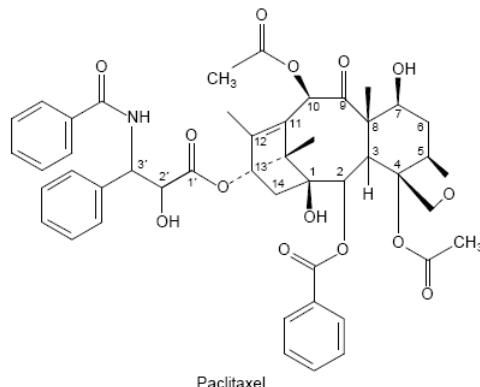
“Plants that Heal”

- Plant derived drug products:
 - >25% prescription drugs are derived from plants
 - >90% of current therapeutic classes from natural product prototype
- Highly Purified Drugs
 - Paclitaxel
 - Artemisinin
- Drug substances as mixtures (partially purified)
 - Psyllium, pyrethrins (OTC)
 - **Veregen** (a partially purified green tea extract)
 - **Fulyzaq** (proanthocyanidins from *Croton lechleri*)

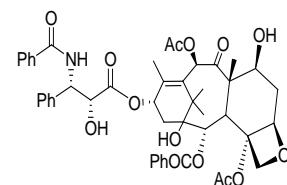
Examples of Plant Derived Purified Small Molecule Prescription Drugs

Plant Derived New and “Pure” Drugs – A Well Known Example

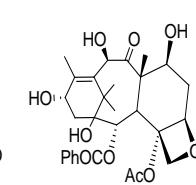
- 1962 Sample of *Taxus brevifolia* (Pacific Yew) collected
 - 1971 Paclitaxel/Taxol structure reported
 - Monroe E. Wall and Mansukh C. Wani
 - 1991 CRADA: NCI – Bristol-Meyers Squibb
 - 1992 FDA approval of Taxol® (an NME) for ovarian cancer
 - 2004 FDA approval of Docetaxel (Taxotere®, Aventis) for prostate C.



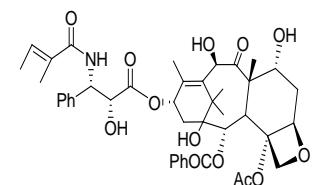
Different *Taxus* Species (Yew Trees) Produce Paclitaxel and 300+ Other Taxanes



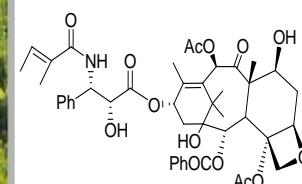
Paclitaxel



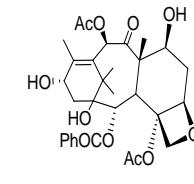
10-Deacetyl baccatin II



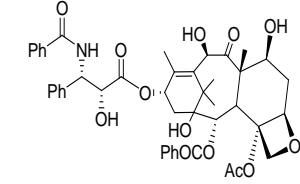
7-*epi*-10-Deacetyl cephalomanine



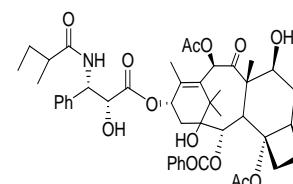
Cephalomanine



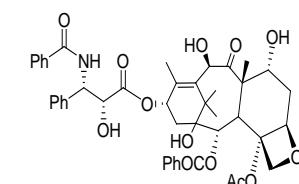
Baccatin I



10-Deacetyl taxol



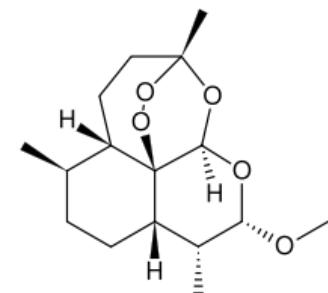
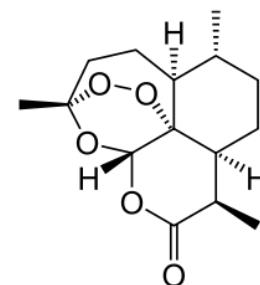
2",3"-Dihydrocephalomanine



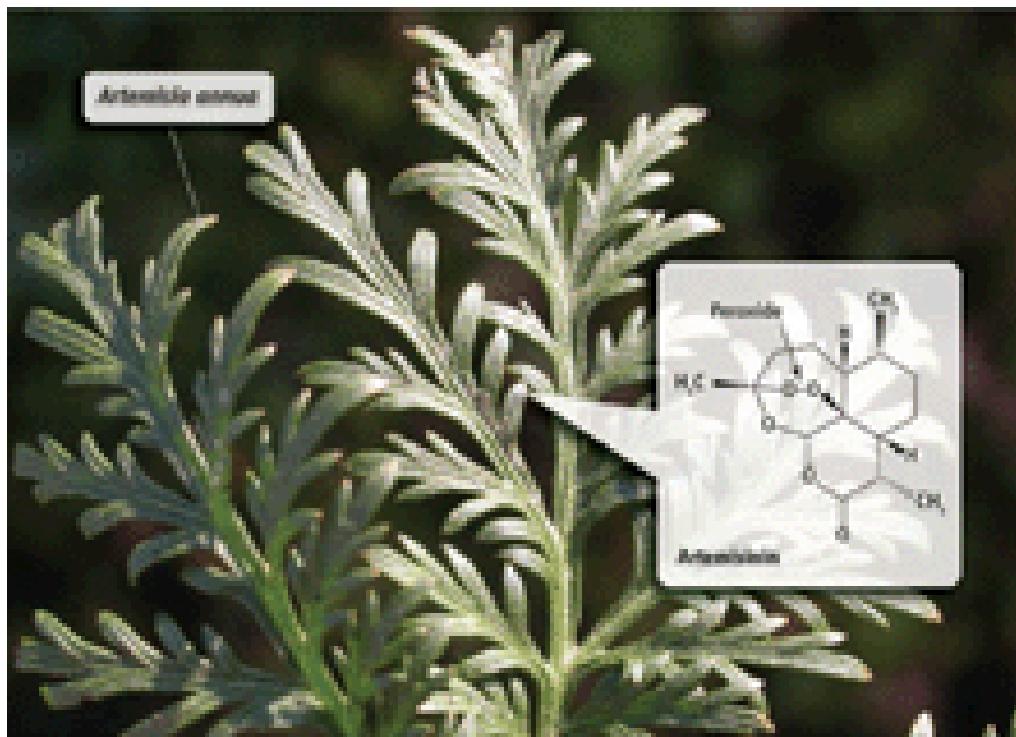
7-*epi*-10-Deacetyl taxol

Artemisinin for the Treatment of Malaria

- *Artemisia annua* L,
 - An herb for the treatment of malaria is in 340 AD
 - Ge Hong in his book Zhou Hou Bei Ji Fang (A Handbook of Prescriptions for Emergencies)
- 1969-1972 Artemisinin (Qinghaosu, 青蒿素, left) was characterized as an active antimalarial compound by Chinese Scientists
 - Leading by Professor Youyou Tu 屠呦呦
 - 1978, National Science Congress Prize, P.R.China
 - 2011, Albert Lasker Award for Clinical Medical Research (for saving millions of children, especially in the developing world)
- WHO Essential medicines-Artemether (right)
 - How much credit should be given to TCM?



Herbal Solution for Malaria?



青蒿

Artemisia annua L.

李时珍 Li Shizheng

<<本草纲目>> (1590)

Compendium of Materia Medica

Collect *Qinghao* leaves
on May 5th (lunar)
Dry in the shade

Treat malaria with
alternating fevers and chills

Take a handful of the leaves, blend
with 2 liters of water

Each dose contains ~ 3 g of the
herb, ...

Clinical Studies of Artemisia Herb as a More Affordable Artemisinin Drug?

Any clinical trials for malaria comparing pure artemisinin with placebo should include a third arm, a tea of *Artemisia annua* (also known as Qing Hao or Sweet Annie),

James Duke, Fulton, MD
Retired USDA Botanist and Herbalist

We recommend that the Gates Foundation, public health officials, and the pharmaceutical industry support the needed pharmacological and clinical trials of standardized *A. annua* teas and other extract

Gordon Cragg (NCI, Chief, Natural Products)
Jorge Ferreira (USDA, Senior scientist/chemist)
et. al, C&EN, 83(18); p4 May 2, 2005

Tanzania, a Wa-arusha man harvests Artemisia

<http://www.sciencemag.org/cgi/content/full/327/5963/279/F1> (2007)





An herbal “solution” for curbing the malaria epidemic?

- WHO Position Statement (June 2012)
 - WHO recommends artemisinin-based combination therapy (ACT) for the treatment of uncomplicated malaria
 - WHO does not recommend the use *A. annua* plant material, in any form, including tea, for the treatment or the prevention of malaria
- Artemisia herb could be **further developed** as a “new” and more affordable artemisinin based botanical drug
 - Ancient Chinese methods are remarkably effective for the preparation of artemisinin-rich extracts of Qing Hao with potent antimalarial activity

Wright, C.W., et al., Molecules 2010
 - **Artemisinin production in *Artemisia annua*: a novel delivery method for treating malaria and other neglected diseases.** Weathers, P.J., et al., Phytochem Rev. 2011
 - Flavonoids from *Artemisia annua* L. as antioxidants and their **potential synergism with artemisinin** against malaria and cancer. Ferreira JF et al. Molecules. 2010 Apr 29;15(5):3135-70.

Examples of Plant Derived OTC Drugs Marketed in the US

Plant Derived Mixtures as OTC Drugs

- Final Monograph
 - Witch Hazel
 - Pyrethrins
- Monograph (Not Final)
 - Psyllium
 - Senna

Plant Derived Mixtures as OTC Drugs: Pyrethrins (除虫菊酯)

[Code of Federal Regulations]

[Title 21, Volume 5]

[Revised as of April 1, 2013]

[CITE: 21CFR358.610]

Pediculicide Drug Products

The active ingredients of the product consist of the combination of **pyrethrum extract** (providing a concentration of **pyrethrins of 0.17 to 0.33 percent**) with piperonyl butoxide (2 to 4 percent) in a nonaerosol dosage formulation.

[63 FR 43303, Aug. 13, 1998]

Plant Derived Mixtures as OTC Drugs: Witch Hazel

21 CFR 347

SKIN PROTECTANT DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

- **347.12(c) Astringent active ingredients**
 - Witch Hazel

Plant Derived Mixtures as OTC Drugs: Senna

- Senna -OTC MONOGRAPH NOT FINAL (Category III)
 - Leaves of SENNA OCCIDENTALIS and other species
 - Lack of safety (carcinogenicity) data for long term use
- Products at National Drug Code Directory
 - E.g., Senna S as a combination of Senna leaf/Sennosides and Sodium Dioctylsulfosuccinate
 - Search Results: Active Ingredient > "Senna"
 - http://www.accessdata.fda.gov/scripts/cder/ndc/dsp_searchresult.cfm

Plant Derived Mixtures as OTC Drugs: Psyllium (also food and dietary supplement)

- Psyllium Husk- OTC MONOGRAPH NOT FINAL (Category III)
 - National Drug Code Directory Active Ingredient > "psyllium"
 - Seeds of *Plantago ovata* and *P. psyllium*
 - Contain soluble fibers as a bulking agent (Laxative)
 - But the granular dosage form (if taken dry or partially dissolved) is NOT generally recognized as safe and effective (GRASE) for causing esophageal obstruction (Category II)
 - Federal Register Volume 72, Issue 60 (March 29, 2007)
 - 21CFR201.319
- 21CFR101.81 Health claims: Soluble fiber from certain foods and risk of coronary heart disease (CHD).
 - 7 g or more per day of soluble fiber from psyllium seed husk “may help to reduce the risk of CHD”

Approved Botanical New Drug Applications (NDAs) in US

The First Botanical NDA Approved under the Guidance

- Brand/Generic name: Veregen/sinecatechins
- Drug substance: Partially purified green tea extract, mainly catechins (~90% by weight) (Japan)
- Botanical raw material: Green tea, the dried leaves of *Camellia sinensis* (China)
- Formulation: 15% Ointment
- Indication: Genital/perianal warts
- Sponsor: MediGene, Inc. (Germany)
- Approval Date: October 31, 2006

Efficacy of Veregen

Table 1 Primary Endpoint Efficacy Results (ITT-LOCF) N (%)

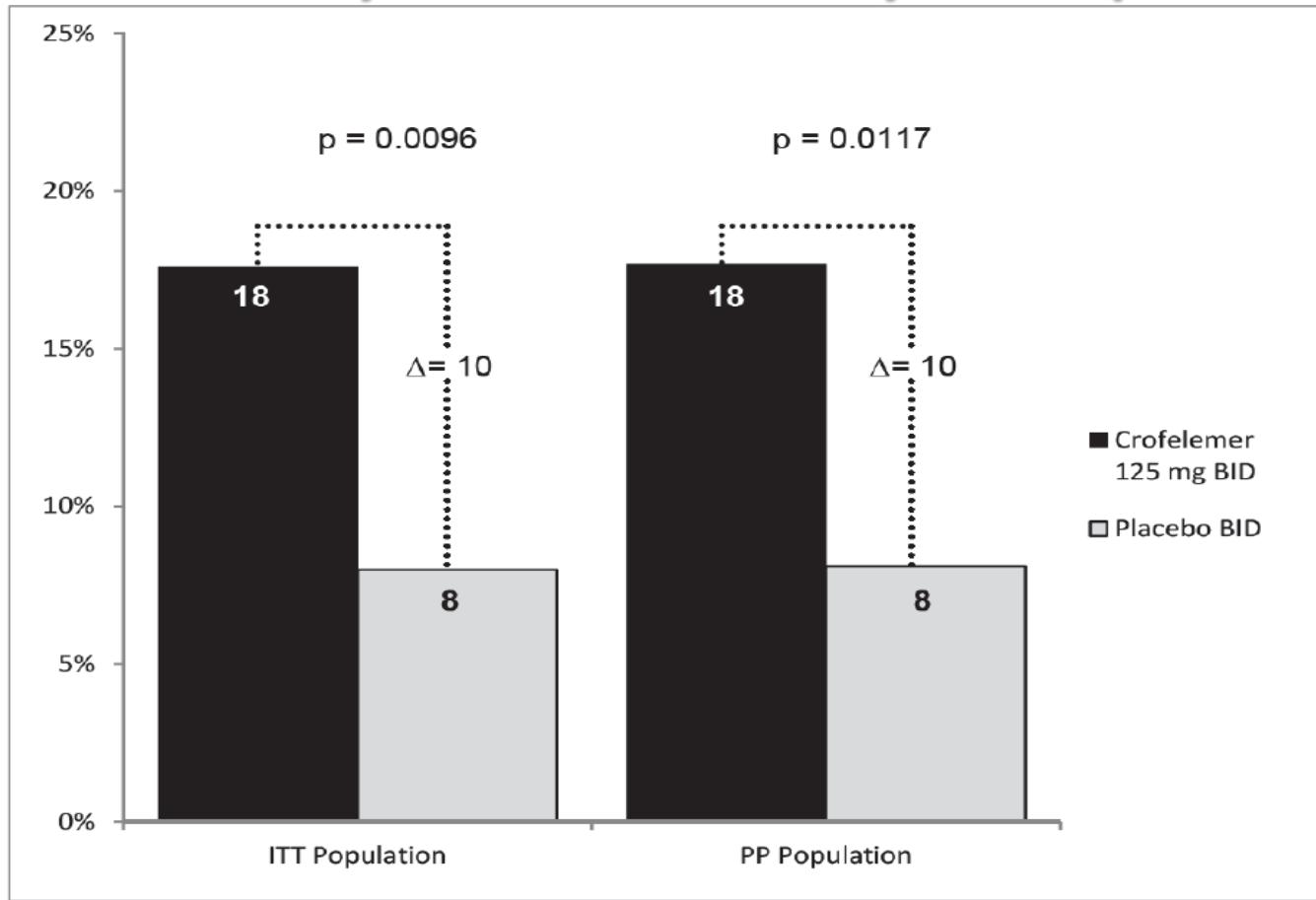
	Study CT 1017			Study CT 1018		
	Vehicle N=103	10% Oint N=199	15% Oint N=201	Vehicle N=104	10% Oint N=202	15% Oint N=196
Success	38 (36.9)	99 (49.7)	102 (50.7)	35 (33.7)	111 (55.0)	111 (56.6)
Fail	65 (63.1)	100 (50.3)	99 (49.3)	69 (66.3)	91 (45.0)	85 (43.4)
p-value	-	0.0384	0.0284	-	<0.001	<0.001

Source: Statistical Reviewer's Analysis using Fisher's exact test.

From Traditional Herbs to Botanical New Drugs

- The 2nd approved botanical NDA (Crofelemer/Fulyzaq, 202292) is for the treatment of HIV related diarrhea
- The 1st approved oral botanical drug
 - Mainly proanthocyanidin oligomers (a subgroup of condensed tannins) with 1000s+ analogs
- The raw material, latex from *Croton lechleri* in South America, has been traditionally used for treating diarrhea
- TCM herbs, containing polyphenols/tannins also used for treating diarrhea
 - As astringents or “涩肠止泻”
- Drug-screening programs aim to find “new potent single drug-like molecules” typically remove those kinds of polyphenols
 - [E.g., Tu Y. J Nat Prod. 2010 Apr 23;73\(4\):751-4. doi: 10.1021/np9007359](#)

Fulyzaq – Clinical Response Rates by the Primary Endpoint



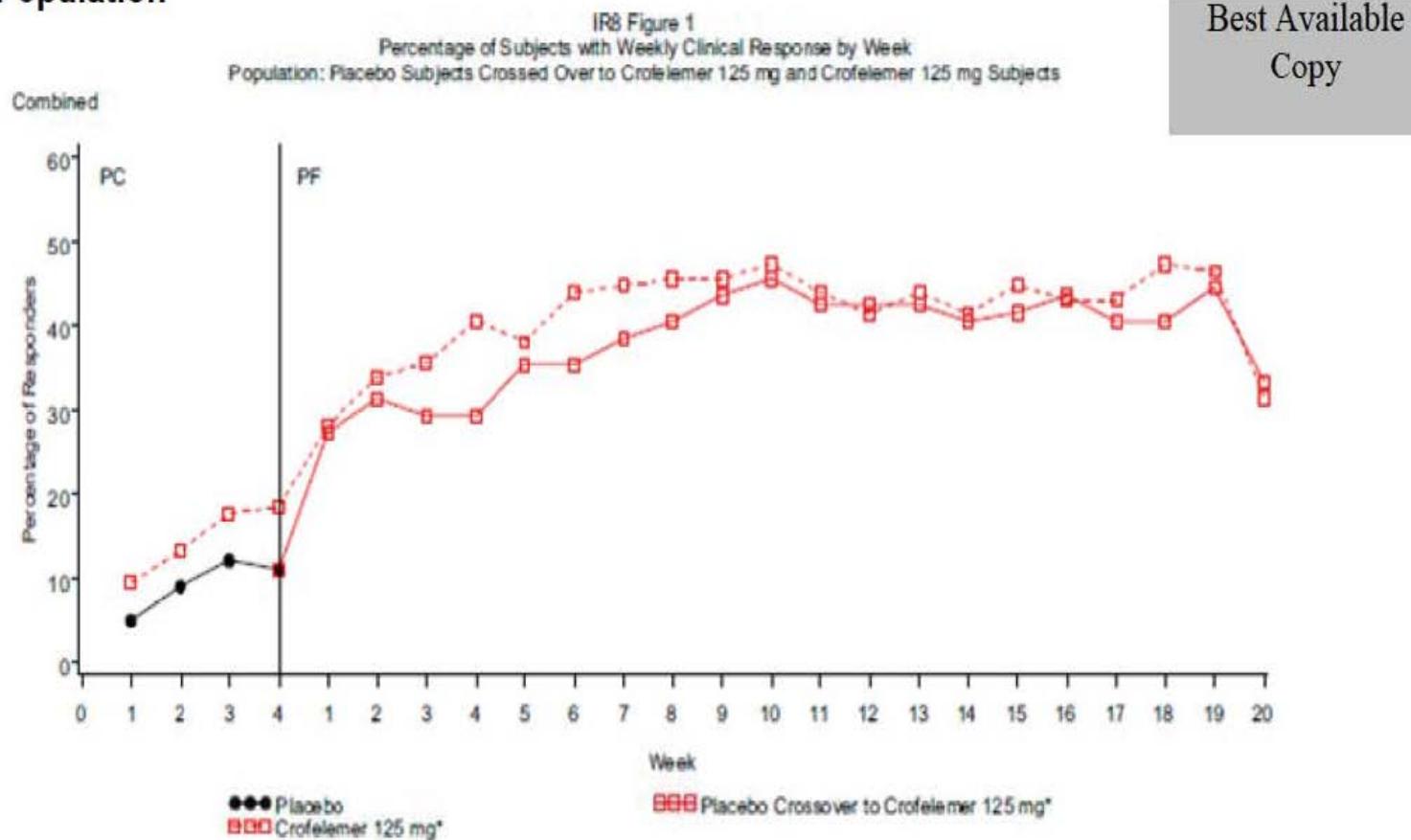
From Section 11.4.1 of the Main Study Report, Page 92

Notes: Clinical response was defined as ≤ 2 watery stools per week during at least 2 of the 4 weeks of the placebo-controlled treatment phase. P-values and CIs were calculated based on the methods of Posch and Bauer.

Fulyzaq – Clinical Response Rates

(Placebo Control and Placebo-Free phase)

Figure 7: Percentage of Subjects with Clinical Response by Week – ITT Population

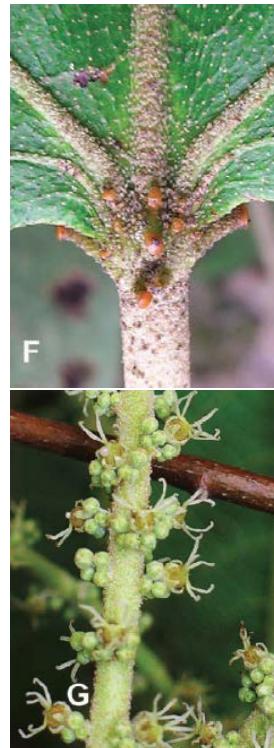


Veregen and Fulyzaq: The BRMs

Veregen (Sinecatechins) Ointment	Fulyzaq (Crofelemer) Tablet
Dried tea leaves (Green tea)	Red latex (Dragon's/Tree's blood)
<i>Camellia sinensis</i>	<i>Croton lechleri</i>
Cultivated in farms in China Variation of catechins in tea varieties/cultivars well-known	Wild collection from South America; Variations of proanthocyanidins not reported in literature
Renewed machine or manual harvest	Trees felled, latex collected manually
2 nd only to water as a soft drink; Tea has been used in TCM, but no traditional application recorded particularly for genital warts	No. 1 herb in Peru for diarrhea and wound healing

Botanical Raw Material of Fulyzaq

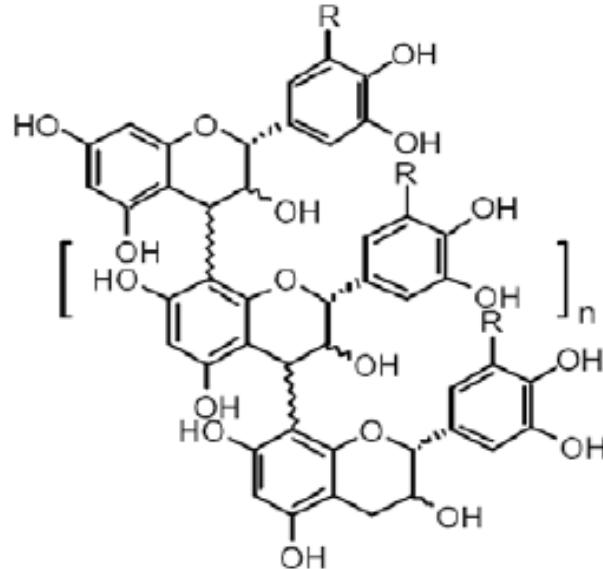
- Photos of *Croton lechleri* Müll. Arg [Euphorbiaceae] and its latex
 - KS Lindner, Blood of the Dragon;
 - van Ee BW, Berry PE. TAXON. 2011; 60 (3): 791–823



Botanical New Drugs: Drug Substances

Fulyzaq (Crofelemer)

4 monomer units: catechin (C), EC; and gallocatechin (G), EG

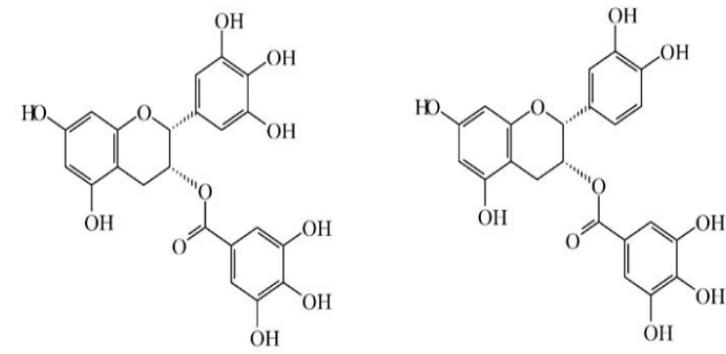
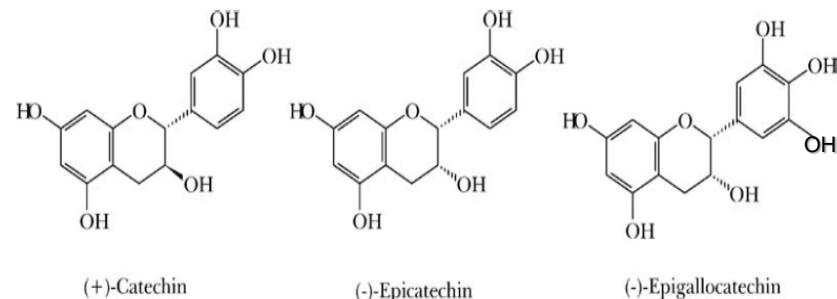


Crofelemer Proanthocyanidins

- n = 1-28 R= H or OH
- 1000s+ of oligomer analogs

Veregen (Sinecatechins)

5 of the 8 Catechins*



*Jeong WS and Kong AT, Pharma Bio. 2004; 42 pp 84-93

Complexity of Crofelemer and Grape Seeds: Estimated possible numbers of proanthocyanidin analogs

	DP*	Crofelemer Oligomers		Grape Seed Oligomers	
		4 Monomers: C, EC, GC, EGC		2 monomers: C and EC	
Dimer	2	$4^2 = (2^2)^2$	16	2^2	4
Trimer	3	$4^3 = (2^2)^3$	64	2^3	8
Tetramer	4	4^4	256	2^4	16
Pentamer	5	4^5	1,024	2^5	32
Hexamer	6	4^6	4,096	2^6	64
Heptamer	7	4^7	16,384	2^7	128
Octomer	8	4^8	65,536	2^8	256
Nonamer	9	4^9	262,144	2^9	512
Decamer	10	4^{10}	1,048,576	2^{10}	1,024
Undecamer	11	4^{11}	4,194,304	2^{11}	2,048
Total			5,592,400		4092

DP* = Degree of polymerization

Fulyzaq (Crofelemer):

Pharmacology and Mechanisms of Action

- **Herbal medicine as an oral anti-diarrheal agent**
 - Products of dragon's blood marketed as dietary supplements
- **Inhibition of two types of intestinal chloride channels**
 - The calcium activated chloride channels (CaCC)
 - The cAMP stimulated cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels
- **Action site: luminal surface of intestine**
- **Bioassay required for NDA approval**

Discussions and Closing Remarks

- Botanical NDA approvals are possible in the 21st Century
 - Both NDAs filled were approved (2/2=100% -😊)
- Challenging issues for developing botanical new drugs will remain
 - How to ensure quality and therapeutic consistency
 - Difficult judgment calls often necessary
 - Products may have different classes of known and unknown components
 - Active and inactive components may be difficult to define

Botanical Drugs: When the mixture works

Or works better than “the magic bullet single compound”

- Veregen drug substance (Sincatechins) contains 8 **tea catechins** and some other components
 - **“United they work” and became the first botanical drug**
 - **“Divided they fail”** (or less effective) based on nonclinical data

Bode, A.M., et al. and Fu, H., et al., Cancer Prev Res (Phila) 2009
- **Fulyzaq/Crofelemer** contains 1000s+ of proanthocyanidin analogs
 - Impossible for becoming a “PURE” single molecule drug
 - **“Together they become a new antidiarrheal drug for HIV patients”**
 - **First-in-class**



Botanicals: A Viable Option for New Drugs

- Could potentially use more molecules of a plant species can offer
 - Additive or even synergistic for certain disease
 - Avoid “bad” interactions with other drugs
- Constructionist vs. Reductionist
 - Single part from a single plant is not a combination
 - “Multiple herb” formulations may need to show contribution of each herb, if feasible
 - Clinical and non-clinical methods



Synergy: An Important Consideration in Botanical Drug Development

Synergy-Directed Fractionation of Botanical Medicines: A Case Study with Goldenseal (*Hydrastis canadensis*)

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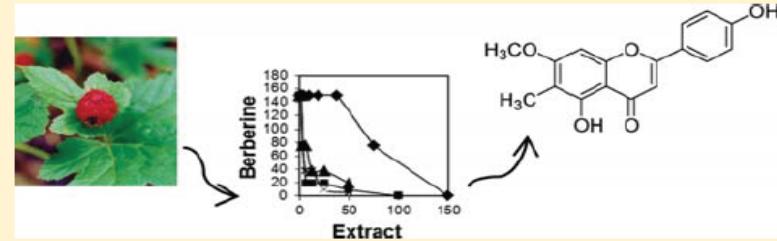
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[‡]Department of Mathematics and Statistics, The University of North Carolina Greensboro, P.O. Box 26170, Greensboro, North Carolina 27402, United States

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S Supporting Information

ABSTRACT: It is often argued that the efficacy of herbal medicines is a result of the combined action of multiple constituents that work synergistically or additively. Determining the bioactive constituents in these mixtures poses a significant challenge. We have developed an approach to address this challenge, synergy-directed fractionation, which combines comprehensive mass spectrometry profiling with synergy assays and natural products isolation. The applicability of synergy-directed fractionation was demonstrated using the botanical medicine goldenseal (*Hydrastis canadensis*) as a case study. Three synergists from goldenseal were identified, sideroxylin (1), 8-desmethyl-sideroxylin (2), and 6-desmethyl-sideroxylin (3). These flavonoids synergistically enhance the antimicrobial activity of the alkaloid berberine (also a constituent of *H. canadensis*) against *Staphylococcus aureus* by inhibition of the NorA multidrug resistance pump. The flavonoids possess no inherent antimicrobial activity against *S. aureus*; therefore, they could have been missed using traditional bioactivity-directed fractionation. The flavonoid synergists are present at higher concentration in extracts from *H. canadensis* leaves, while the antimicrobial alkaloid berberine is present at higher levels in *H. canadensis* roots. Thus, it may be possible to produce an extract with optimal activity against *S. aureus* using a combination of goldenseal roots and leaves.



Online Resources

- **FDA Website**
 - FDA approves first anti-diarrheal drug for HIV/AIDS patients-Fulyzaq
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333701.htm>
 - Drugs@fda
- **Traditional Chinese Medicine: An Introduction at NCCAM**
<http://nccam.nih.gov/health/whatiscam/chinesemed.htm>
- **PubMed Cited Journal Publications on**
 - Green tea polyphenols and EGCG
 - Goldenseal and berberine alkaloid (whole herb more active than the purified alkaloid as antibacterial agent)
 - Artemisia and Artemisinin
 - Removal of polyphenols/tannins pre-screening
- **Key word search at the following websites**
 - <http://en.wikipedia.org/wiki/>
 - <http://www.baidu.com/> (in Chinese)
 - <https://www.google.com/>
 - <http://www.chinaculture.org/> (articles on TCM)



In Loving Memory of My Father

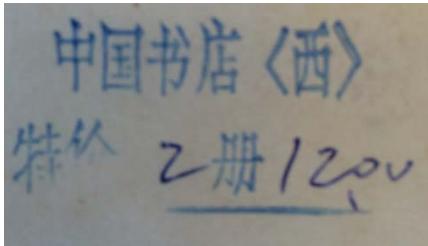
Mr. Zhiguang Dou

(April 10, 1935 – February 19, 2012)

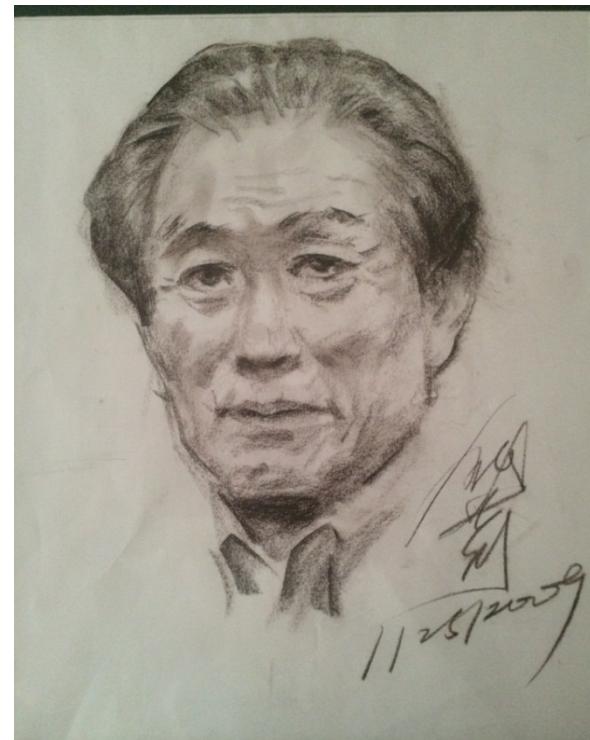
“I will Keep working and enjoy what I do while alive”



“The Encyclopedia of Chinese Herbs” (left)
A gift from dad in 1984,
when I became a graduate student of Pharmacognosy.



Portrait of Mr. ZG Dou (right) by a Chinese artist.



THANK YOU



