Development of Botanicals as New Drugs:
Update and Review Experience from US FDA

Jinhui Dou, Ph.D.
Charles Wu, Ph.D.
Sau Larry Lee, Ph.D.

Botanical Review Team (BRT)
Office of Pharmaceutical Quality (OPS), CDER, FDA

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Disclaimer

Opinions expressed in this presentation are those of the presenter's and do not necessarily reflect the views or policies of the FDA.

Outline

- "Plants that Heal"
  - Herbal medicines and plant-derived pure drugs
- Botanical Guidance
  - Support R&D of plant-based mixtures as botanical drugs
- Botanical Drug Review Experience in CDER FDA
  - Investigational New Drugs
  - Challenges of bring a botanical drug to market through an NDA
    - Botanical Guidance is revised to emphasize on late phase drug development
- "Food for Thought" on Botanical Drug

"Plants that Heal"

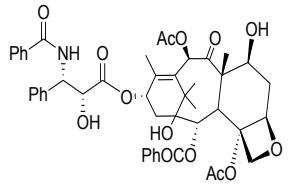
- Plant derived drug products as a class:
  - **>25% of all prescription drugs**
  - >90% of current therapeutic classes from natural product prototype

    Newman DJ, Cragg GM. J Nat Prod. 2007 Mar;70(3):461-77.

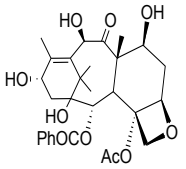
- Plant-derived single molecule drugs
  - Paclitaxel and analogs
  - Artemisinin and analogs

- Plant-derived mixtures as drugs
  - Psyllium, pyrethrins (OTC)
  - Veregen (a partially purified green tea extract)
  - Fulyzaq (proanthocyanidins from *Croton lechleri*)

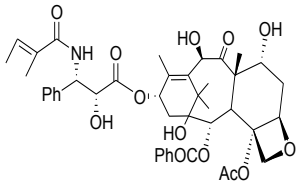
Taxus Species Produce over 300 Taxanes



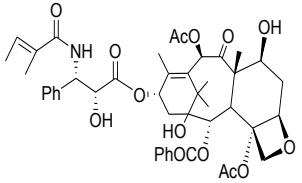
Paclitaxel



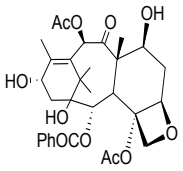
10-Deacetyl baccatin III



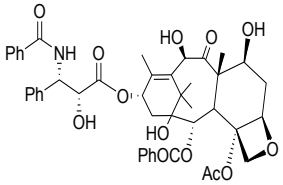
7-*epi*-10-Deacetyl cephalomanine



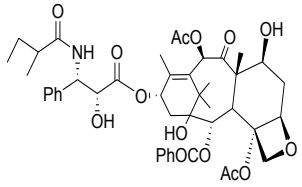
Cephalomanine



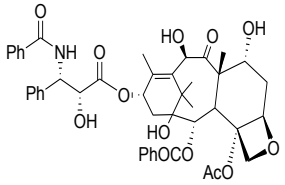
Baccatin III



10-Deacetyl taxol



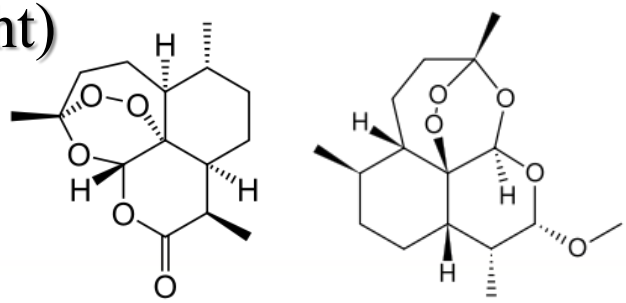
2",3"-Dihydrocephalomanine



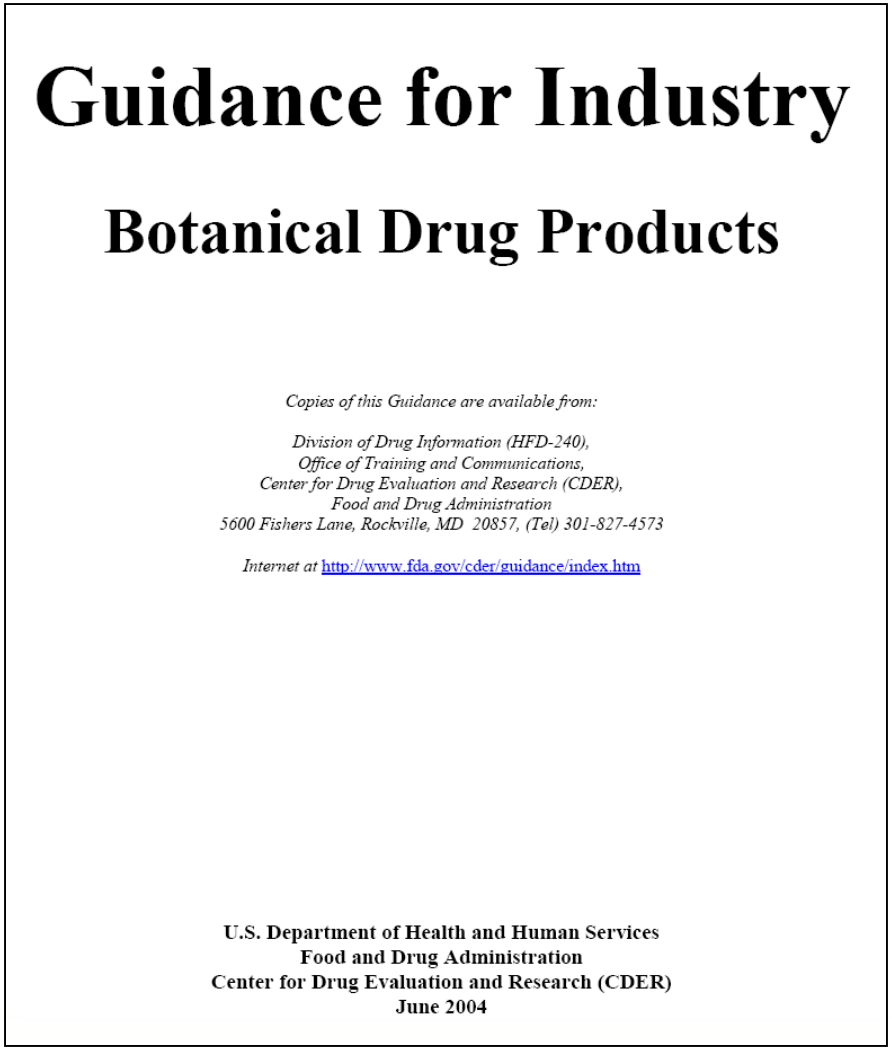
7-*epi*-10-Deacetyl taxol

Artemisinin for the Treatment of Malaria

- *Artemisia annua* L., **An herb for** the treatment of malaria
  - Recorded in 340 AD in "Zhou Hou Bei Ji Fang" (A Handbook of Prescriptions for Emergencies) by Ge Hong
- Artemisinin (Qinghaosu, left) was discovered in1969-1972
  - Professor Youyou Tu, the key developer of artemisinin
    - 2011, Albert Lasker Award for Clinical Medical Research
- WHO Essential medicines-Artemether (right)



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

(* Revision will be published for comment soon)

Other CDER guidance

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

Botanical Drug Product:

A product that contains as ingredients vegetable materials, which may include plant materials, algae, macroscopic fungi, or combinations thereof, that is *used as a drug*. It may be available as (but not limited to) a solution (tea, e.g.), powder, tablet, capsule, elixir, topical or injectable.

Excluded: fermentation products, highly purified [or chemically modified] botanical substances, genetically modified plants, allergenic extracts and vaccines which contain botanical ingredients

Botanical Guidance-Basic Principles (1)

- Flexibility on certain CMC requirements
  - Identification of active constituents in the botanical is not essential
  - Further purification not required (but encouraged)
    - The importance of botanical raw material quality control is emphasized
- Prior human use may substitute for animal toxicology studies
  - Non-clinical evaluations may be reduced or delayed for certain botanicals entering phase 1/2 clinical trials

Botanical Guidance-Basic Principles (2)

- Adequate and well-controlled trials are necessary for marketing botanical drugs in the US
  - Multiple-dose and multiple-batch for demonstration of "therapeutic consistency" is emphasized in the revised Guidance document
- Same level of overall clinical efficacy/safety requirements as non-botanical drugs for NDA approval
  - The risk/benefit analysis approach will be the same for botanical and non-botanical drugs

Pharmacognosy Review of Botanical Drugs

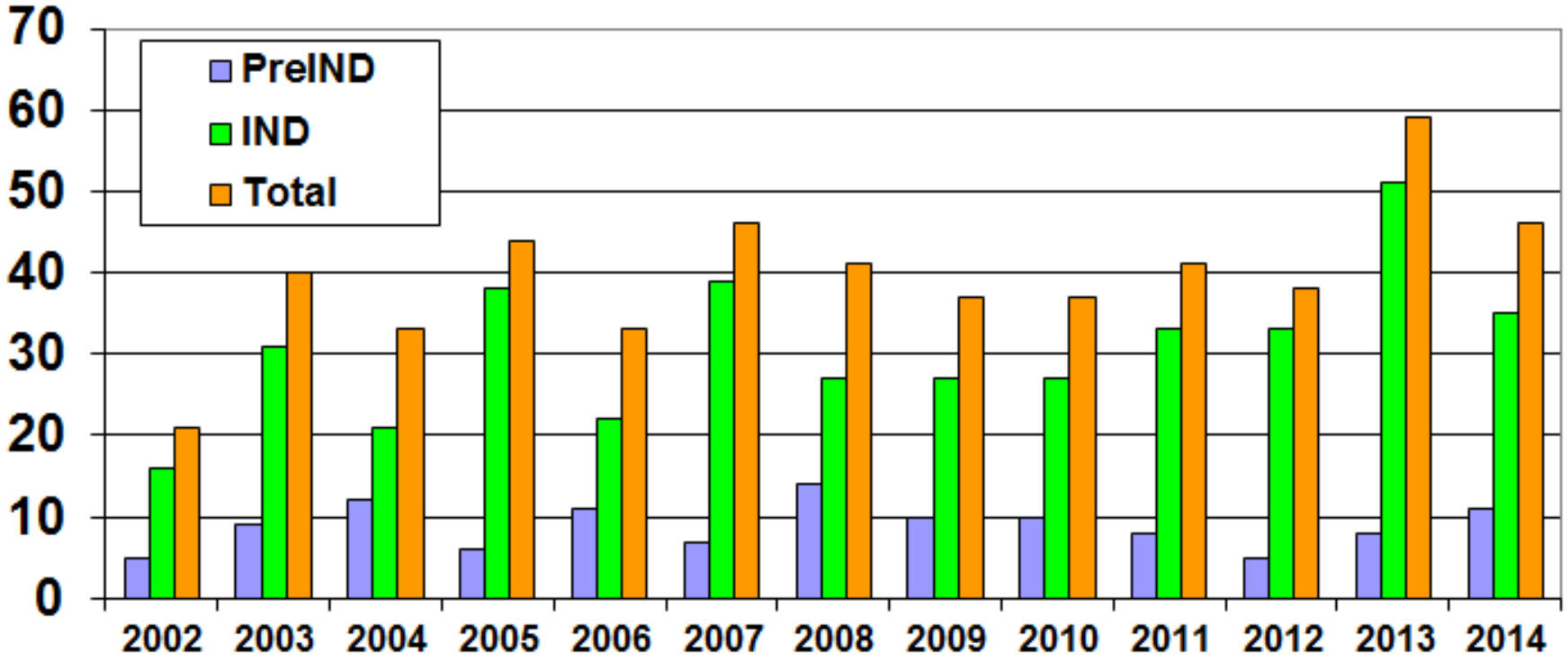
- Medicinal plant biology
  - Identification, potential misuse
- Pharmacology of botanical drugs
  - Old theories and new testing
- Prior human experiences
  - Mostly in complementary and alternative medicine (CAM), systems such as TCM
- More
  - Ensuring quality and therapeutic consistency

Botanical Drug Review Experience in CDER FDA

Botanical Applications in CDER, FDA (as of December 31, 2014)

- Over 600 pre-INDs/INDs submitted to CDER
  - Approximately 2/3 single herb, 1/3 multiple herb INDs
  - Approximately 1/3 commercial INDs, 2/3 research INDs
- Mostly phase 2, and a few in Phase 3
  - Most of the new drug review divisions in OND have a few botanical INDs/pre-IND
  - Significant number of botanicals INDs for studying Chinese herbs
- Two NDAs submitted and approved

Botanical IND Applications by Year (2002-2014)



Long Journey from IND to NDA (1)

- Veregen ® (Sinecatechins/Polyphenon® E)
  - Submitted on September 30, 2005
  - NDA 021906 (approved on October 31, 2006)

- IND 56,401 (submission dates ?, but before 1996)

- Polyphenon® E (a standardized green tea extract) was commercialized in 1983

Long Journey from IND to NDA (2)

- Fulyzaq ® (crofelemer)
  - NDA 202292 (approved on December 31, 2012)
    - Submitted on December 5, 2011

- IND 58,818 (Submitted on November 1, 1996)
  - Antiviral activity of crofelemer (SP-303) was reported in 1991

Veregen NDA in a Nutshell

- 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 (respond rates)

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.

The Second Botanical NDA

- Brand/Generic name: Fulyzaq/Crofelemer
- Botanical raw material/drug substance: crude plant latex of *Croton lechleri* ("Dragon's Blood")
- Formulation: 125 mg oral tablet
- Indication: HIV related diarrhea
- Sponsor: Salix Pharmaceuticals
- Approval Date: December 31, 2012

Efficacy of Fulyzaq (Crofelemer)

Parameter/Statistic[a, b]	Crofelemer 125 mg BID n (%)	Crofelemer 250 mg BID n (%)	Crofelemer 500 mg BID n (%)	Placebo BID n (%)
Responder – n/N (%)	9/44 (20.5%)	5/54 (9.3%)	9/46 (19.6%)	1/50 (2.0%)
Treatment Difference	18.5%	7.3%	17.6%	---
1-sided 97.5% CI for Diff.	[6.0%, ∞)	[-1.7%, ∞)	[5.3%, ∞)	---
1-sided p-value (vs. placebo)	0.0019	0.0563	0.0024	---

Clinical Response (intent-to-treat population), from NDA Medical Review (available in Drugs@FDA)
Clinical response was defined as ≤ 2 watery stools per week during at least 2 of the 4 weeks of the placebo-controlled treatment phase.

a. p-values and CIs were calculated based on the methods of Posch and Bauer (2005).

b. If less than 5 days of data were available in a week, the subject was classified as a non-responder for that week. Subjects who discontinued prematurely during the 4-week period were classified as nonresponders. Subjects who used an ADM or opiate pain medication for > 3 days during the efficacy assessment period were also non responders.

Veregen and Fulyzaq: The BRMs

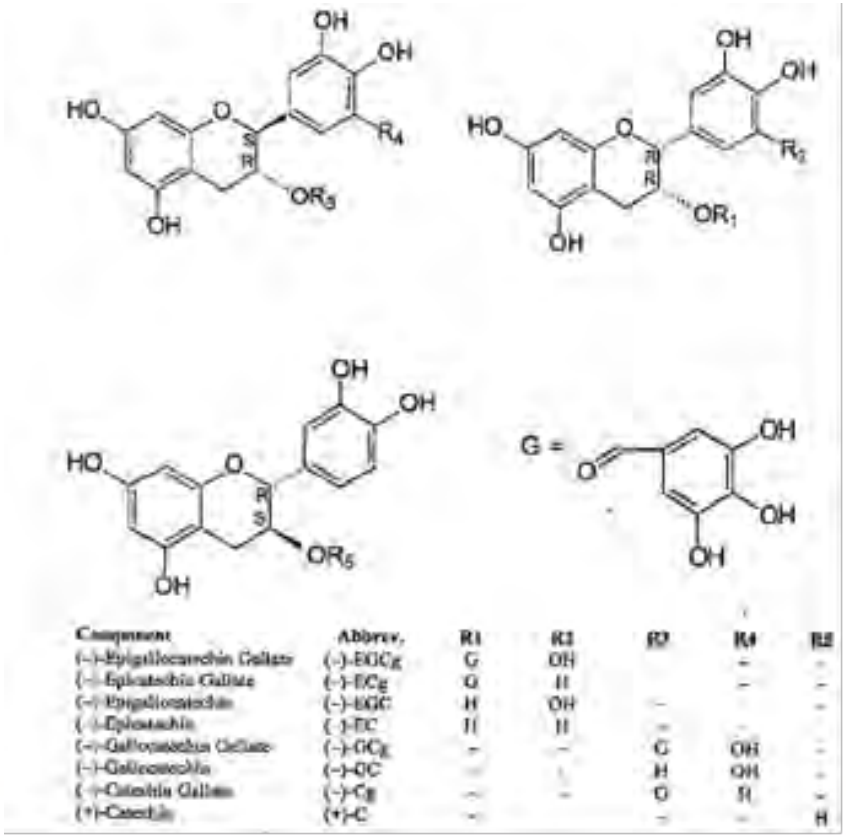
Veregen (Sinecatechins) Ointment	Fulyzaq (Crofelemer) Tablet
Dried tea leaves (Green tea)	Red latex (Dragon's/Tree's blood)
Camellia sinensis (L.) Kuntze [Theaceae]	*Croton lechleri* Müll. Arg [Euphorbiaceae]
Cultivated in farms in China Variation of catechins in tea varieties/cultivars well-known	Wild collection from South America; Variations of proanthocyanidins unknown; but expected to be less prominent due to lack of human intervention
Renewed machine or manual harvest	Trees felled, latex collected manually
2nd only to water as a soft drink; No traditional use recorded for genital warts	No. 1 herb in Peru for diarrhea and wound healing

Veregen and Fulyzaq – The BDSs

Sinecatechins	Crofelemer
"The drug substance as a whole is the active component"	Proanthocyanidin oligomers with degree of polymerization (DP) 3-14 (30) as the major "active" molecules
8 Catechin monomers: Individually purified and fully characterized, well resolved by HPLC	Total proanthocyanidin oligomers assayed, but individual oligomers or groups (e.g., trimers, tetramers, etc) not well separated by HPLC
Major catechin (EGCG) : >55% Other minor components controlled	Acid hydrolysis and other methods to measure average monomer units in oligomers and mean MW; Catechin, EC, GC, EG ratios
Unknown mechanisms of actions No bioassay	Known mechanisms of action reported Required bioassay(s) for consistency

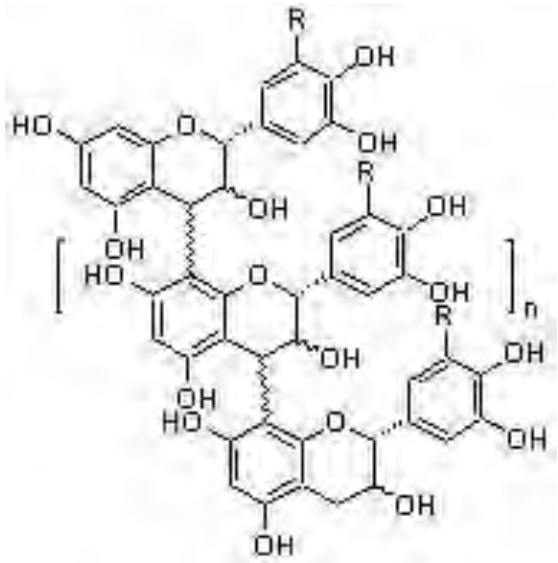
Veregen and Fulyzaq: Major Catechins and Proanthocyanidins in the Drug Substances

Catechin monomers in Sinecatechins



Component	Abbrev.	R1	R2	R3	R4	R5
(−)-Epigallocatechin Gallate	(−)-EGCg	G	OH		–	–
(−)-Epicatechin Gallate	(−)-ECg	G	H		–	–
(−)-Epigallocatechin	(−)-EGC	H	OH	–		–
(−)-Epicatechin	(−)-EC	H	H	–	–	–
(−)-Gallocatechin Gallate	(−)-GCg	–	–	G	OH	–
(−)-Gallocatechin	(−)-GC	–	–	H	OH	–
(−)-Catechin Gallate	(−)-Cg	–	–	G	H	–
(+)-Catechin	(+)-C	–	–	–	–	H

Proanthocyanidins in Crofelemer



R = H (C and EC) or
R= OH (GC and EGC)
Average range n = 3 to 5.5
(n = 1-28 as literature reported)

Ensure Therapeutic Consistency for the Fulyzaq NDA (1)

- Extend CMC control to raw material
  - Latex of an easily identifiable single plant species
  - GACP and Eco-geographic regions established
  - Testing/Processing of raw material
- Conventional CMC
  - Characterization "adequate" *for a complex natural mixture, but*
    - Further molecular details difficult due to nature of the botanical and technical limitation
    - *Some difficulties in quantification remain*

Ensure Therapeutic Consistency for the Fulyzaq NDA (2)

- Non-CMC information to support therapeutic consistency
  - Extensive human use to treat diarrhea
  - Clinical response not appear to be sensitive to dose/lot variations
    - Mechanism: closing of chloride channels saturated at clinical doses
  - Bioassay

Lessons Learned from the Botanical NDAs (1)

- Demonstration of safety and efficacy through well-controlled clinical trials for botanical drugs are the same as other drugs
- An integrated approach for NDA review was applied
  - Raw material controls required
  - Comprehensive conventional CMC approaches to monitor the downstream processes and the physiochemical profiles of intermediates, substances, and products with meaningful specifications are necessary to demonstrate and ensure chemical consistency
  - Non-CMC data, e.g., bioassay, may be used to ensure batch-to-batch consistency, as needed
- Clinical trials can be used to demonstrate therapeutic consistency
  - Multiple-batch study useful for establish drug specifications
  - Multiple-dose study may support certain levels of variations (unknowns) in the drug substance/product tolerable

Lessons Learned from Botanical NDAs (2)

New therapies from old medicines

Shaw T Chen, Jinhui Dou, Robert Temple, Rajiv Agarwal, Kuei-Meng Wu & Susan Walker

Although new botanical drugs pose many challenges for both industry and the FDA, approval of the first botanical prescription drug shows they can be successfully met.

Green tea leaves are the source for sinecatechins, the active ingredients of Veregen—the first botanical product to be approved as a prescription drug by the FDA.

http://www.nature.com/nbt/journal/v26/n10/pdf/nbt1008-1077.pdf

Evolution of traditional medicines to botanical drugs

Authors: Sau L. Lee*, Jinhui Dou*, Rajiv Agarwal, Robert Temple, Julie Beitz, Charles Wu, Andrew Mulberg, Lawrence X. Yu, Janet Woodcock

Botanicals constitute an important source for new drugs (*1*, *2*). To facilitate botanical drug development, the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA) established the Botanical Review Team in 2003 and published its first *Guidance for Industry: Botanical Drug Products* in 2004 (*3*). This guidance represents FDA's thinking and provides recommendations on quality, nonclinical, clinical, and other unique aspects associated with botanical new drug development through the investigational new drug (IND) and new drug application (NDA) processes. From 2004 to 2013, CDER received over 400 botanical IND applications and pre-IND meeting requests (Table 1). Most of the INDs were allowed to enter phase 2 clinical trials for evaluation of preliminary safety and efficacy of the investigational botanical products in patients. FDA approved the first botanical NDA for Veregen (sinecatechins) in 2006 (*4*, *5*) and the second botanical NDA for Fulyzaq (crofelemer) in 2012 (*6*, *7*). These two NDA approvals show that new therapies

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Science 2015 Jan 16;347(6219 Suppl.):S32-4

http://www.sciencemag.org/site/products/collectionbooks/TCM_Jan_16_2015_high%20res.pdf

Food for Thought: Botanical Drug Solutions ?

Consideration of Botanical Drugs (1): Following the leads of human experience

- Dragon's blood has been commonly used for treating diarrhea in Peru and other countries in South America
  - Other herbs (e.g., TCM herbs) containing polyphenols (e.g., condensed tannins) also used as anti-diarrhea agents
    - "Polyphenols as astringent agents to stop diarrhea" （涩肠止泻）
- Artemisinin discovery initiated from Artemisia's TCM use for malaria treatment
  - Dried-leaf Artemisia annua: A practical malaria therapeutic for developing countries? Weathers PJ et al. World J Pharmacol. 2014 ;3(4):39-55.

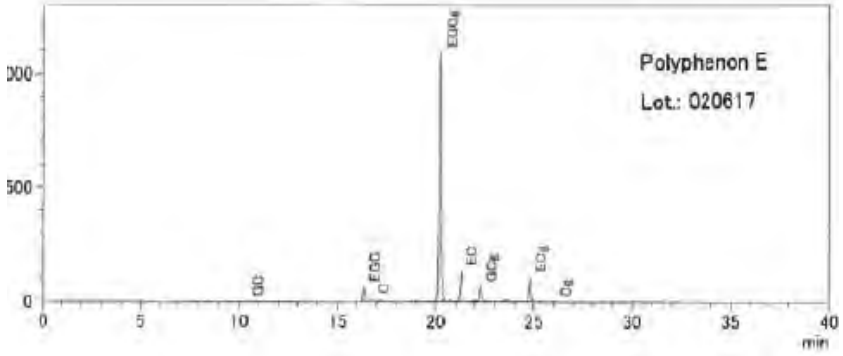
Consideration of Botanical Drugs (2): Taking advantages of synergy or additive effects

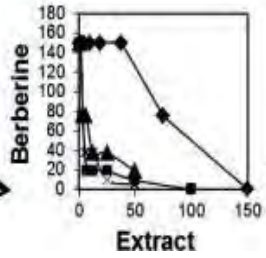
- Lung cancer inhibitory effect of epigallocatechin-3-gallate is dependent on its presence in a complex mixture (polyphenon E).

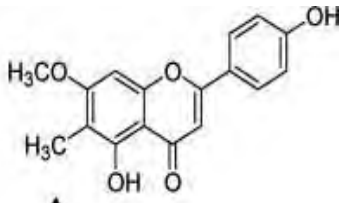
  Fu H, You M. et al. Cancer Prev Res (Phila). 2009 Jun;2(6):531-7.

  - Epigallocatechin 3-gallate and green tea catechins: **United they work, divided they fail**. Bode AM, Dong Z. Cancer Prev Res (Phila) 2009

- Synergy-directed fractionation of botanical medicines: a case study with goldenseal (*Hydrastis canadensis*). Junio HA, Oberlies NH et al. J Nat Prod. 2011 Jul 22;74(7):1621-9.







Consideration of Botanical Drugs (3):
"A silver bullet" approach may be impractical

- Crofelemer may contain millions of proanthocyanidin oligomer molecules (e.g., trimers to 30mers reported)
  - Polyphenols often removed pre-screening for causing false-positive when a pure active molecule was the target
  - Separation of proanthocyanidin oligomer into single purified active molecules impractical
    - Trimers alone may have up to 64 (i.e., 4^3) very similar analogs

Consideration of Botanical Drugs (4):

More **affordable new drugs** ?

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

Cragg G, Ferreira J. et. al,
C&EN, 83(18); p4 **May 2, 2005**

Dried-leaf *Artemisia annua*: A practical malaria therapeutic for developing countries? Weathers PJ et al. *World J Pharmacol.* **2014** ;3(4):39-55.

Tanzania, a Wa-arusha man harvests **Artemisia**, a Chinese herb used for treating **malaria** for ages

http://www7.nationalgeographic.com/ngm/0707/feature1/gallery1.html
http://ngm.nationalgeographic.com/**2007**/07/malaria/stanmeyer-photography

THANK YOU!

Lindner, KS. The Sustainable Harvest and Replanting of the ***Croton lechleri* Tree**. HerbalGram 84, 57-65, 2009

Current Core members of CDER BRT

- Sau (Larry) Lee, Ph.D.
  Sau.Lee@fda.hhs.gov
  Associate Dir. & Team Leader
- Jinhui Dou, Ph.D.,
  jinhui.dou@fda.hhs.gov
  Pharmacologist & Pharmacognosist
- Charles Wu
  charles.wu@fda.hhs.gov
  Pharmacologist