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 Pryrethrins
    • 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):
  – Post-Doc with Drs. Les Mitscher and Michael Jung

• 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)
  – Expert of botanical drug review in OPS, CDER
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 of natural origin as well as the search for new drugs from natural sources"
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
5800 Fishers Lane, Rockville, MD 20857; (Tel) 301-827-4573

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

Final guidance published on 06/09/2004

Other CDER guidance*

* 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

共享单车 is 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
    – 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** 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 (朱橚, 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
  – State Administration of Chinese Medicine
  – MOST (Ministry of Science and Technology) and MOH

• 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

• US NIH (ODS and NCCAM) support TCM research as “dietary supplements” and “complementary alternatively medicines”
  – Challenges of ensuring safety for some herbal medicines as “dietary supplements”
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, was credited to use 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**
  - Drug claims also permitted
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 (Mahuang) 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 symptoms contradicted with Mahuang’s use)

- Ephedra species
  - Chinese Pharmacopeia listed *E. sinica, E. intermedia, E. macropholia* under Mahuang
    - Chinese Ephedra contain ephedrine and pseudoephedrine at more than 1%
  - US species (e.g. *E. nevadensis and E. 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 grams 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
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 drug products
  - 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 – Well Known Examples

- 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), a simple semi-synthetic paclitaxel derivative, for prostate C.
Taxus Plant Species (Yew Trees) Produce Paclitaxel and 300+ Other Taxanes
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 antimonial 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).

**Tanzania, a Wa-arusha man harvests Artemisia**

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

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*
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 may 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
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

[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"
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 (%)

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

Source: Statistical Reviewer's Analysis using Fisher's exact test.
From Traditional Herbs to Botanical New Drugs

• The 2\textsuperscript{nd} approved botanical NDA (Crofelemer/Fulyzaq, 202292) is for the treatment of HIV related diarrhea

• The 1st FDA approved oral botanical drug
  – Mainly proanthocyanidin oligomers (a subgroup of condensed tannins) with 1000s+ analogs

• The raw material, latex from \textit{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
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.

Dr. Wenyi Gao’s review http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202292Orig1s000Approv.pdf
Fulyzaq – Clinical Response Rates
(Placebo Control and Placebo-Free phase)

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

Best Available Copy
### Veregen and Fulyzaq: The BRMs

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

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

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

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 by FDA
Discussions and Closing Remarks

• Botanical NDA approvals are possible in the 21\textsuperscript{st} Century
  – Both NDAs were approved (2/2=100\% -\ding{192})

• 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

• 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 NME
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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**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 alkaloids
  – Artemisia and Artemisinin
  – Removal of polyphenols/tannins pre-screening

• Key word search at the following websites
  – 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 my father in 1984, when I became a graduate student of Pharmacognosy.

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