Natural Products. A History of Success and Continuing Promise for Drug Discovery and Development

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EARLY DOCUMENTATION OF USE OF MEDICINAL PLANTS


• Mesopotamian ~2,600 B. C. E.
• Egyptian ~ 1,800 B. C. E.
• Chinese – ~1,100 B. C. E. and continuing
• Indian ~ 1,000 B. C. E. and continuing
• Greek ~ 500 B. C. E.

Greco-Roman expertise preserved and coordinated with other traditions by Islamic cultures during the Dark Ages ~ 400-1,100 CE

Avicenna. Persian pharmacist, physician, poet, philosopher author: canon medicinae – “final codification of Greco-Roman medicine”

Great Moments in Pharmacy Collection APhA
Traditional Medicine and Drug Discovery

• 80% of the world population resides in developing countries
• 80% of people in developing countries utilize plants to meet their primary health care needs
• Global pop. ca. 7 billion → ca. 4.5 billion people utilize plants to meet their primary health care needs

1800s. Discovery of some active principles of major herbal preparations

European chemists (apothecaries) revolutionized drug discovery and development.

1817. Sertürner reports isolation of morphine from *Papaver somniferum*. Commercialized by E. Merck in Darmstadt in 1827

1820. Pelletier & Caventou – quinine from *Cinchona* species

1820. Pelletier & Caventou – colchicine from *Colchicum autumnale* and codeine (*P. somniferum*)

1832. Robiquet – codeine from *Papaver somniferum*

1839. Pirai – salicylaldehyde from *Salix* species, converted to salicylic acid. Acetyl salicylic acid synthesized by Gerhard in 1853. Developed at Bayer as the drug, aspirin, in 1899.

1848. G. F. Merck – papaverine from *P. somniferum*.

1875. Schmiedeberg – digitoxin from *Digitalis purpurea*
ANTIMALARIAL DRUGS – THE ROLE OF TRADITIONAL MEDICINE


Quinine from Cinchona spp. used in the Amazon region for centuries for treatment of fevers

Artemisinins from Artemisia annua used in TCM for centuries for treatment of fever - developed for the treatment of drug resistant malaria.
MORPHINE – AN INDISPENSABLE PAINKILLER
Isolated from *Papaver somniferum*

Morphine: $R_1 = R_2 = H$
Codeine: $R_1 = CH_3 ; R_2 = H$
Heroin: $R_1=R_2=COCH_3$

Oxycodone
In clinical use since 1917
Cone snails pioneered a combinatorial library strategy to evolve highly bioactive venom peptides targeting cell surface receptors or ion channels.

Ziconotide isolated from *Conus majus* for treatment of intractable neuropathic pain

- Potent activity against voltage-gated Ca\(^{2+}\) channels
- Approved by FDA in Dec. 2004. Marketed as Prialt®
- Application limited due to difficult delivery via intrathecal infusion from reservoir in peritoneum.

**Synthesis of orally bioavailable cyclic analogs (e.g, cVc1.1)**


120 times more potent than gabapentin in animal models in the treatment of neuropathic pain.
VENOMS AS SOURCES OF POTENTIAL ANALGESICS

King, Expert Opin. Biol. Ther., 2011, 11, 1469-1484

Pain: Targets - e Na\textsubscript{v}1.7, 1.8 and 1.9 voltage-gated sodium ion channel subtypes found in peripheral nervous system. Na\textsubscript{v}1.7 is the most ‘exciting’ analgesic target. 6 other subtypes found in brain, heart, and muscle tissue.

Halford, C&EN, 2014 (Mar. 24), 92 (12), 10-14

µSLPTX. From venom of the Chinese red-headed centipede *Scolopendra subspinipes mutilans*: potent, selective blocker of Na\textsubscript{v}1.7 channel.


Protoxin-1. From venom of the Peruvian green-velvet tarantula, *Thrixopelma pruriens*. Spider-venom peptides are generally potent, but not selective, sodium channel blockers

Klint, King et al., Toxicon, 2012, 60, 478–491.
Herbal use to treat polyuria (excessive urination) associated with Type 2 diabetes. Metformin decreases hyperglycemia primarily by suppressing liver glucose production. Also being developed for treatment of cancer. Leone et al., Cancer Treat. Res. 2014, 159, 355-76.


Mimics natural incretin hormones that stimulate the release of insulin in response to a meal. FDA approved use in 2005 but is investigating possible increased risk of pancreatitis and pre-cancerous cellular changes/pancreatic duct metaplasia

http://www.fda.gov/drugs/drugsafety/ucm343187.htm
THE MICROBIAL WORLD OF BACTERIA AND FUNGI

SOURCE OF CHEMICAL DIVERSITY AND WONDER DRUGS

Alexander Fleming – serendipitous discovery of penicillin in 1928

Lentinus edodes (Berk.) Sing.

• Penicillins (*Penicillium spp.*); cephalosporins (*Cephalosporium acremonium*); glycopeptides, tetracyclines, polyketides (*Streptomyces spp.*)

• Immunosuppressive agents: Cyclosporin, rapamycins (*Streptomyces spp.*)

• Cholesterol-lowering agents: Mevastatin, lovastatin, etc. (*Penicillium spp.*)

• Anticancer drugs: Anthracyclines (e.g., doxorubicin), bleomycins, mitomycins, staurosporins (*Streptomyces spp.*); epothilones (*Myxobacteria*)

Penicillins (*Penicillium spp.*).

Penicillin G
Structure 1945

Thienamycin is resistant to β-lactamases. Its discovery formed the basis for the synthesis of many carbapenems which have been a last resort in the treatment of many drug resistant bacterial infections.

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<tr>
<th>Structure</th>
<th>Description</th>
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<tr>
<td><img src="image" alt="Penicillin G" /></td>
<td>Penicillin G Structure 1945</td>
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<tr>
<td><img src="image" alt="6-Aminopenicillanic acid" /></td>
<td>6-Aminopenicillanic acid. Basis for synthesis of multiple penicillin analogs</td>
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<tr>
<td><img src="image" alt="Thienamycin" /></td>
<td>Thienamycin, <em>S. Cattleya</em> 1976</td>
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<tr>
<td><img src="image" alt="Carbapenem" /></td>
<td>Carbapenems</td>
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Cephalosporins (Cephalosporium acremonium)


Estimated that well over 20,000 penicillin and cephalosporin-based molecules have been produced by semi- and total syntheses based on 6-aminopenicillanic acid and 7-amino-cephalosporanic acid.
Glycopeptides and Polyketides

Vancomycin *(Amycolatopsis Orientalis)*
1955-6

Semi-synthetic derivatives: Oritavancin, Telavancin/FDA approved 2009, Dalbavancin/ approved by FDA May 23, 2014, both for treatment of skin infections

Erythromycin *(Streptomyces erythreus)*
1952

Cethromycin (Restanza) EDP-420.
Tetracyclines

Petković et al., Genetics of *Streptomyces rimosus*, the oxytetracycline producer. Microbiol. Mol. Biol. Rev. 2006 Sep;70(3):704-28;

Tetracycline (*Streptomyces viridifaciens*) ($R_1 = R_2 = \text{OH}; R_3 = \text{H}$) 1955
Aureomycin (*S. aureofaciens*) ($R_1 = \text{Cl}; R_2 = R_3 = \text{H}$) 1945
Oxycycline (*S. rimosus*) ($R_1 = R_2 = R_3 = \text{OH}$) 1950
Doxycycline (semisynthetic) ($R_1 = \text{OH}; R_2 = \text{H}; R_3 = \text{OH}$) 1962

Tigecycline (Tygacil)

Antifungal Antibiotics

Amphotericin 1955
Cereghetti and Carreira Review
Synthesis, 2006, 6, 914-42

Echinocandin class. Active against infections caused by Aspergillus and Candida species refractory to amphotericin.
FDA approved 2001
A Bacterial Battle. Bacteria are Outsmarting Us!
Jarvis, C&EN, 2014 (June 16), 92(24), 9-14

Antibiotic Resistance Factors

- Inactivation of antibiotics by enzymatic reactions (e.g., inactivation of β-lactams by β-lactamase)
- Efflux mechanisms by which antibiotics are transported out of cells by pumps (e.g., tetracyclines subject to tet M efflux pumps)
- Target mutation to decrease binding efficiency of antibiotics (e.g., modification of D-Ala-D-Ala to D-Ala-D-Lac making vancomycin less effective)
- Overproduction of target (e.g., DHFR)
- Bypass of the metabolic pathway to remove the essentiality of the target (e.g., peptide deformylase in Streptococcus pneumonia)
- Decreased uptake of antibiotics (e.g., Pseudomonas aeruginosa loss of its D2 porin)

16 papers covering Aminoglycosides, Antifolates, Antitumor antibiotics, Glycopeptides and Lipoglycopeptides, β-Lactams, Lantibiotics, Macrolides and polyketides, Streptogramins and Oxazolidinones, Quinolones and pyridones, Rifamycins, Thiopeptides.

CHOLESTEROL LOWERING DRUGS
The Birth of the Statins – A Valuable Gift from Nature

Atorvastatin (Lipitor)
FDA approval 1996

Compactin: \( R_1 = R_2 = H \); from *Penicillium centrinum*, Endo et al., *J. Antibiot.*, 1976, 29, 1346-1348
Lovastatin: \( R_1 = H, R_2 = CH_3 \); from *Aspergillus terreus*, FDA approval 1987; Alberts et al., *Proc. Natl. Acad. Sci.*, 1980, 77, 3957-3961
Simvastatin: \( R_1 = R_2 = CH_3 \); FDA approval 1991
Pravastatin: \( R_1 = H, R_2 = OH \); FDA approval 1991

Akiro Endo
Biopharm Res.
Labs., Japan

HO
CO
SCoA
NADPH
H^+

HO
CO
H
SCoA
NADPH
H^+

80; HMGCoA Reductase Mechanism
Mevalonate

HO
CO
OH
SCoA
NADPH
H^+

HO
CO
OH
SCoA
NADPH
H^+

Compactin: \( R_1 = R_2 = H \); from *Penicillium centrinum*, Endo et al., *J. Antibiot.*, 1976, 29, 1346-1348
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Atorvastatin (Lipitor)
FDA approval 1996
ANTITUMOR ANTIBIOTICS


Doxorubicin (Adriamycin)
*S. peucetius* 1969
FDA approval 1974
Semisynthetic derivs:
Epirubicin. FDA approval, 1999
Idarubicin (Idamycin). FDA approval, 1990

Dactinomycin (Actinomycin D)
*S. antibioticus* 1940; FDA approval 1964

Mitomycin C.
*S. caespitosis* 1960
FDA approval 1974

Bleomycin (Blenoxane)
*S. Verticillus* 1966
FDA approval 1973

Federico Arcamone
Naxospharma
Milan

Selman Waksman
Rutgers Univ.

Hamao Umezawa
Inst. Microb. Chem. Japan
• 1972: Rapamycin (sirolimus) discovered by Brazilian researchers as an antifungal agent.
• Immunosuppressive properties / transplant surgery. Rapamune. FDA approval 1999
• Cancer:
  - Everolimus approved for treatment of brain, breast, pancreatic and renal cancers. 2012
  - Temsirolimus approved for renal cancer. 2007
  - All are in clinical trials against various cancers ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).
• Used in stents to avoid plaque formation and aid blood circulation.
• Shows potential for the treatment of Huntington’s disease, fungal meningitis and other infections associated with contaminated compounding solutions reported in 2013
EPOTHILONES FROM SLIME MOLDS (MYXOBACTERIA)


Eight epothilone analogs have been introduced into cancer clinical studies

Epothilone B (patupilone, Novartis) in phase III clinical trials for ovarian cancer

Epothilone B-Lactam (Ixabepilone, Ixempra) FDA approved for treatment of advanced and metastatic breast cancer resistant to taxanes and anthracyclines. 2007
Epoxomicin isolated from an *Actinomycete* strain 1992.

CYANOBACTERIA – A CONTINUING SOURCE OF PROMISING DRUG LEADS


Cryptophycin A (Cryptophycin 1): R = H
Cryptophycin 52 (LY355703): R = CH₃

Dick Moore
A pioneer in cyanobacterial drug discovery

Cryptophycin 52 entered Phase II Clinical Trials but dropped due to toxicity and lack of efficacy.
Vinblastine: $R = \text{CH}_3$ 1959
Velban FDA approval 1965
Vincristine: $R = \text{CHO}$ 1961
FDA approval 1963

Vinorelbine (Navelbine)
Semisynthetic. Potier group
FDA approved 1994

Vinflunine
Semisynthetic
EMA approved 2009
SEMISYNTHETIC ANALOGS OF PODOPHYLLOTOXIN ISOLATED FROM MEDICINAL *PODOPHYLLUM* SPECIES

TAXOL®. MULTIDISCIPLINARY INTERNATIONAL COLLABoration

Pacific Yew
Taxus brevifolia

Bristol Myers Squibb/NCI CRADA 1989
FDA approval 1992 (ovarian); 1994 (breast)

Mansukh Wani, Monroe Wall
Research Triangle Institute
Isolation from bark of T. brevifolia 1971

Susan Horwitz
Albert Einstein
School of Med.
Unique
MOA 1979

Peter Wiernik, Our Lady of Mercy
Med. Center.
Pioneered
slow infusion. 1983

Pierre Potier, CNRS, France.
Pioneered semisynthesis
from 10-deacetyl baccatin isolated
from leaves of T. baccata. 1988

Eric Rowinsky
Johns Hopkins U.
Efficacy in refractory ovarian
cancer. 1989

Arthur Barclay, USDA
First bark collection, 1962

Pacific Yew
Taxus brevifolia
• Treatment of breast, ovarian and non small cell lung cancers, Kaposi sarcoma. 2,014 clinical trials ongoing (www.clinicaltrials.gov; July, 2014).

• Docetaxel: Similar treatment profile, but easier to formulate/administer. Potier, CNRS; Rhône-Poulenc Rorer (now Sanofi-Aventis). 1,717 clinical trials ongoing (July, 2014). FDA approval 1996.

• Cabazitaxel and an albumin-stabilized nanoparticle formulation of paclitaxel, Abraxane® (nab-paclitaxel, ABI-007) are also approved. FDA approvals: 2010 and 2012, respectively.

• 4 other taxanes (e.g., larotaxel) in Phase III clinical trials. Five analogs and five new formulations are in Phase II and I trials. 14 in preclinical development.

• Low-dose paclitaxel seems promising in treating non-cancer diseases, such as skin disorders, renal and hepatic fibrosis, inflammation, axon regeneration, limb salvage, and coronary artery restenosis. (Zhang et al., Drug. Des. Devel. Ther., 2014, 8:279-84).
CAMPTOTHECIN AND SEMISYNTHETIC ANALOGS


Camptothecin
Isolation from *Camptotheca acuminata* reported 1966

Topotecan (Hycamptin)
Semisynthesis 1991
FDA approval 1996

Irinotecan (CPT-11; Camptosar)
Semisynthesis 1991
FDA approval 1996

Belotecan
Semisynthesis 2000

Camptotheca acuminata
Combretastatins


CA4: $R = H$
CA4-P: $R=\text{PO}_3^{2-} (\text{Na}^+)\_2$

CA4-P (Zybrestat) granted FDA and EMA orphan drug status for treatment of for treatment of anaplastic thyroid cancer (2003/FDA & 2004/EMA) and ovarian cancer (2006/FDA & 2013/EMA)

CA1: $R = H$
CA1-P: $R=\text{PO}_3^{2-} (\text{Na}^+)\_2$

CA1-P granted FDA orphan drug status for treatment of Acute Myelogenous Leukemia (AML). 2012
HOMOHARRINGTONINE AND INGENOL METABUTATE


Homoharringtonine (Synribo; Omacetaxine)
Isolated from *Cephalotaxus harringtonia* by Powell USDA group. 1970
FDA approval for treatment of chronic myeloid leukemia. 2012

Ingenol metabutate (Picato)
Isolated from *Euphorbia peplus* 2004
FDA approval for treatment of actinic keratosis lesions. 2012
Isolation from *Ecteinascidia turbinata* reported independently by Rinehart and Wright in 1990.

FDA granted orphan drug status for treatment of soft tissue sarcoma in 2004 and ovarian cancer in 2005.; in clinical trials against a range of other cancers including breast, ovarian, pancreatic and prostate.
Halichondrin B (HB): Isolation from *Halichondria okadai* in 1985, and later from *Phakelia carteri*, *Axinella sp.* and a *Lissodendoryx* sp. off New Zealand. Following total synthesis of HB, eribulin was identified as the optimal candidate for clinical development. It was approved as Halaven by the FDA in 2010 for the treatment of refractory breast cancer. Currently in clinical trials against several other cancers, mainly in combination with other agents.
Some Marine-Derived Agents: In Past or Ongoing Clinical Trials

**Hemiasterella minor**
South Africa

**Aplidium albicans**
Mediterranean

**Elysia rufescens**
Hawaii

**Discodermia species**
Grand Bahamas

**Bugula neritina**
California

Maytansanoids. Targeted Delivery

Trastuzumab (herceptin)–DM1 conjugate (Kadcyla) approved by FDA in Feb., 2013, for treatment for Her2+ late stage (metastatic) breast cancer.

Other DM1 Antibody Drug Conjugates (ADCs) are in Phase I and II clinical trials (breast, leukemias, lymphomas, gastric, small-cell lung)

Maytansine isolated in the 1960s by Morris Kupchan from Maytenus buchanii and serrata. Too toxic in clinical trials to develop further. Ansamitocins related to maytansine isolated from Actinosynnema pretiosum which is possibly endophytic to the original plant.
Dolastatins. Targeted Delivery


Conjugation to the humanized anti-CD30 monoclonal antibody SGN-30 gives brentuximab vedotin (Adcetris®), directed against the CD30 antigen expressed on Hodgkin lymphoma and anaplastic large cell lymphoma. FDA approved, 2011.
(http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4013484/)

(http://www.crcnetbase.com/isbn/9781439813829)


NEW FRONTIERS
Exploration of extreme environments

• Marine sediments.
  Potts & Lam, Mar. Drugs., 2010, 8, 835-880

• Thermophiles. Deep-sea vents; Hot springs
  http://deepseacenter.rutgers.edu/index.html
  Lutz, McPhee et al., J. Nat. Prod., 2011, 74, 842-846

• Psychrophiles. Arctic/Antarctic/Alpine lakes
  Margesin et al., Environ. Technol., 2010, 31, 835-44

• Toxic lakes and dump-sites
  Berkeley Pit Lake - Butte, Montana
NEW FRONTIERS
Microbial Symbionts

• Endophytic fungi
Kharwa, Stierle et al., Anticancer compounds derived from fungal endophytes: their importance and future challenges. Nat. Prod. Rep., 2011, 28, 1208-1228

• Marine microbial symbionts

• Insect microbial symbionts
Currie, Clardy et al., Bacterial symbionts in agricultural systems provide a strategic source for antibiotic discovery. J. Antibiot., 2014, 67, 53-58
Crawford and Clardy, Bacterial symbionts and natural products. Chem. Commun. (Camb), 2011, 47, 7559-7566
GENOME MINING
Journal of Industrial Microbiology & Biotechnology
Volume 41, Issue 2, February 2014
Special Issue: Microbial Genome Mining
Dedicated Sir David Hopwood

26 articles: Bachmann, Balz et al., Microbial genome mining for accelerated natural products discovery: is a renaissance in the making? : 175-84; Demain, Importance of microbial natural products and the need to revitalize their discovery. : 185-201; Jensen, Fenical, Moore et al., Challenges and triumphs to genomics-based natural product discovery. : 203-9; Diminic et al., Evolutionary concepts in natural products discovery: what actinomycetes have taught us. :211-7; Aigle, Spiteller, Challis et al., Genome mining of Streptomyces ambofaciens. : 251-63; Challis, Exploitation of the Streptomyces coelicolor A3(2) genome sequence for discovery of new natural products and biosynthetic pathways. :219-32
DRUG DISCOVERY

AND

INTERNATIONAL COLLABORATION

Johnson Jato, Cameroon

Ahsana Dar and Iqbal Choudhary & colleagues, Univ. Karachi, Pakistan

Leticia Costa Latufo, Odorico DeMoraes and Claudia Pessoa, Federal Univ. Ceara, Fortaleza, Brazil. Collaboration with many Brazilian groups in antitumor screening
Taxol®

Huge untapped Brazilian resources – how many new drugs await discovery?

Vanderlan Bolzani
COLLABORATION – THE KEY

Phil Crews, UCSC

Bill Gerwick, Scripps Oceanographic Inst.

Lohi Matainaho
University of Papua New Guinea
Major Collaborator
With
Several groups

Ray Andersen
U. Br. Columbia

David Sherman, U. Wisconsin, Madison

Chris Ireland, Louis Barrows (U. Utah) and Lohi Matainaho
THANK YOU

Wortmannin

Penicillium wortmanii

Daunorubicin (R=H) and Doxorubicin (R=OH)

Streptomyces peucitius

Jorumycin

Jorunna funebris

Taxol

Taxus brevifolia bark