1. Introduction to the Chemistry of Natural Products

RA Macahig

FM Dayrit

SY 2012-2013, Summer

"And the earth brought forth grass, and herb yielding seed after his kind, and the tree yielding fruit after his kind, whose seed was in itself, and after his kind: and God saw that it was good."

-Genesis 1:12

What are "Natural Products"?

Chemical characteristics

- Naturally-occurring small organic compounds
  - including heterocyclic compounds, and peptides.
  - does not include proteins, carbohydrates, and nucleic acids.
- MW: ~150 ~ <800 amu ("small molecule")
- Methods of extraction and purification are generally similar to the techniques used for organic compounds

  (e.g., TLC, column chromatography, HPLC, GC)
- Methods of structural determination
  - NMR, MS, IR, X-ray, UV

What are "Natural Products"?

Biological characteristics

• Compounds are generally characteristic of a particular species or family, i.e., narrow taxonomic distribution (non-ubiquitous)

• No nutritional or structural function. Functional roles may include:

- color (identification) - scent (attraction or repulsion)
- sexual attraction - social communication
- defense (e.g., plant toxins and antibiotics)

but many still have unknown function in the organism in which they are found.

• Classified as "secondary metabolites" in contrast to "primary metabolites"

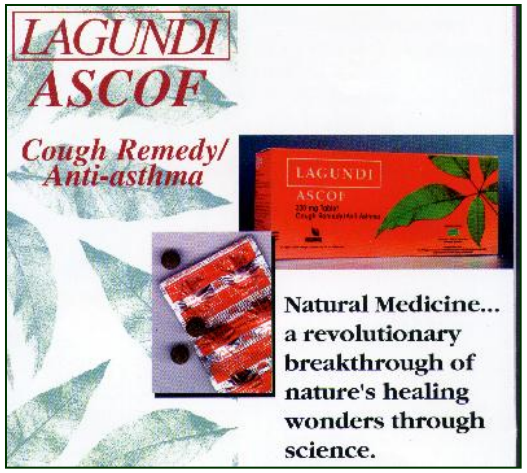
Diverse aspects of the Chemistry of Natural Products:

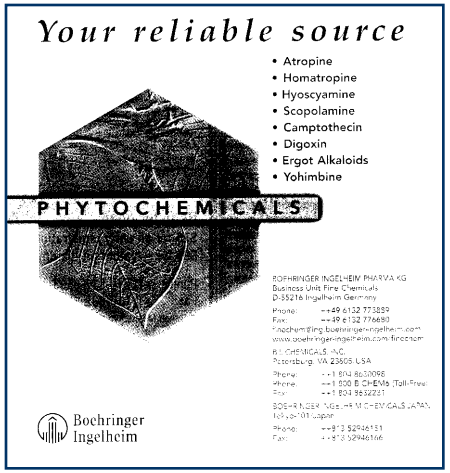
- Structural determination of natural products compounds
- Total synthesis or semi-synthesis of natural products; enzyme synthesis
- Determination of biosynthetic pathways using using plant tissues, cell culture and isotopic labeling
- Pharmaceutical science: pharmacologic effects
- Functional foods, herbal medicines
- Agricultural science: antipest, allelopathy, IPM
- Ethnobotany
- Plant chemistry and plant development
- Biodiversity and Ecology; Marine natural products
- Chemotaxonomy and genetic classification
- Genomics and metabolonomics

Why study Natural Products?

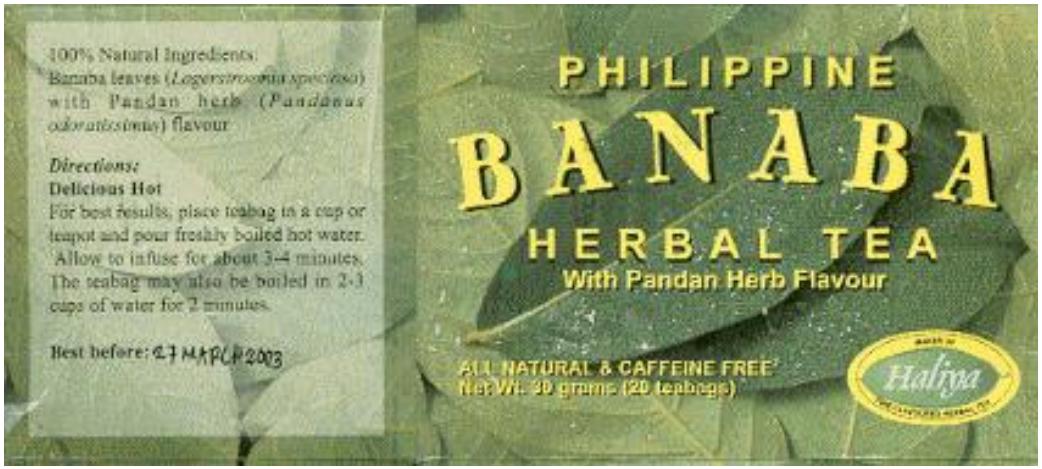
- Natural products are the source of the most complex and fascinating chemical structures.
- Natural products represent biological diversity.
- Natural products are expressions of the genome.
- Natural products represent natural biological activity, whether as single compounds or as complex mixtures.
- Natural products are part of the natural wealth of the country, and can be an important source of livelihood, from agriculture and food, pharmaceuticals, fine chemicals industry.
- Natural products can be an effective bridge from tradition to modern scientific developments, including genetics, molecular biology, biotechnology, and pharmaceutical science.

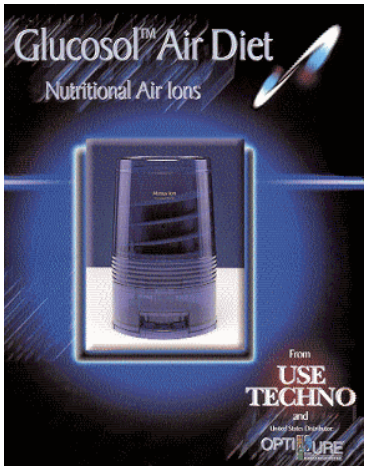
Range of products from natural products:





Range of products from natural products:





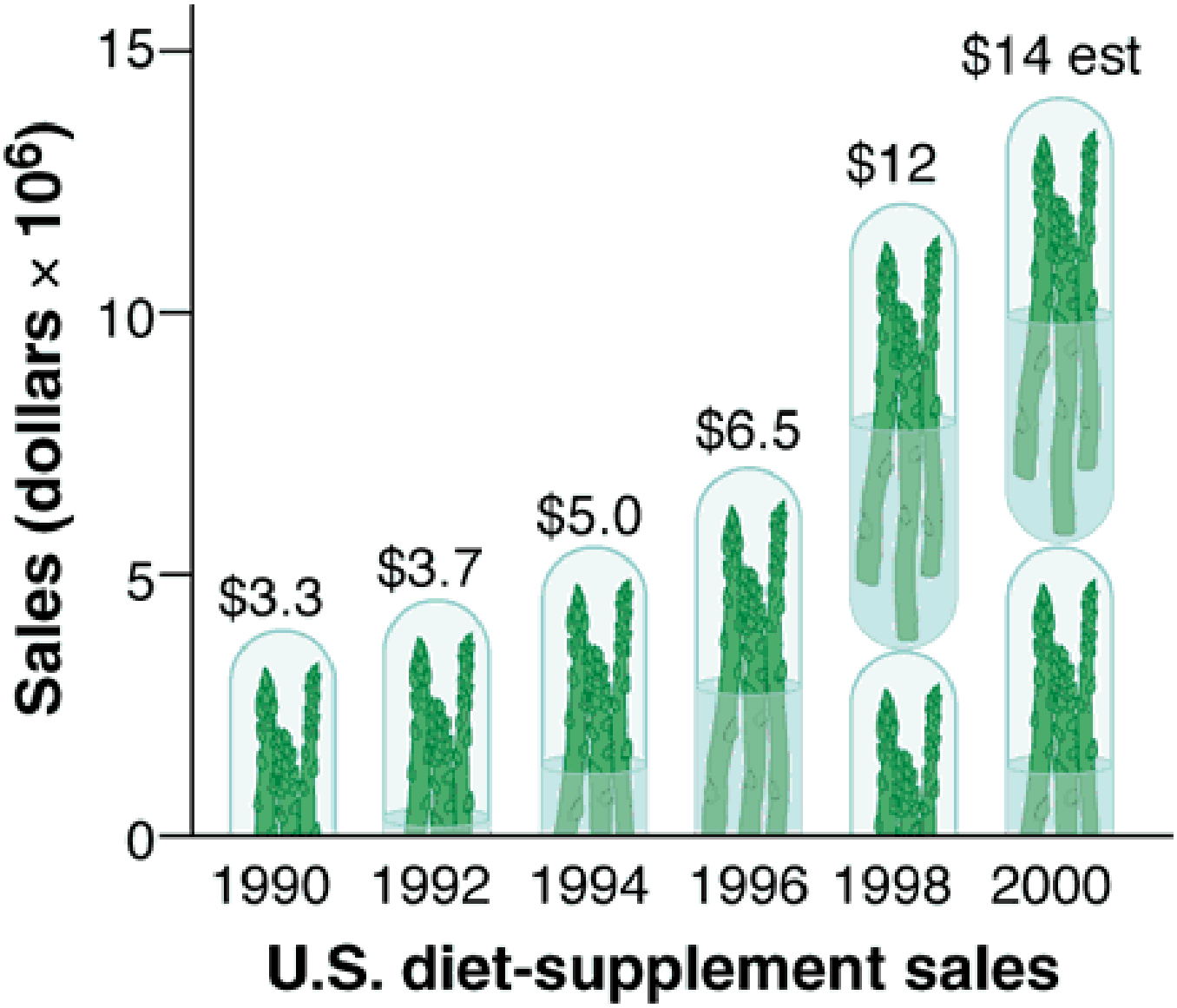
The market for natural products is **HUGE**

- Pharmaceuticals
- Traditional herbal medicines:

  US and Europe: gingko biloba, St. John's wort, ginseng, garlic*, echinacea, saw palmetto, soya*, kava-kava, golden seal, aloe*, gotu kola* (*also grown in the Philippines)

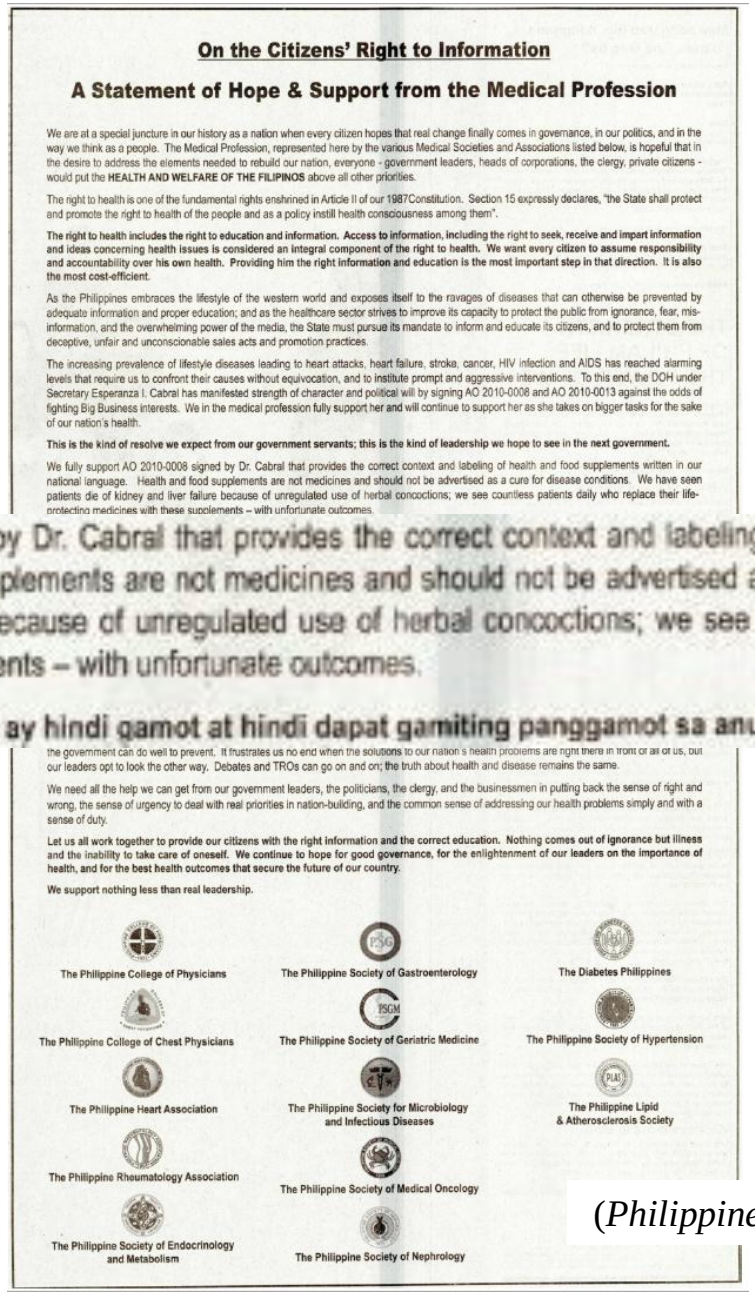
  India, China, Japan: Ayurverda, TCM, Kampo

  Philippines: lagundi, sambong, ampalaya, banaba, malunggay
- Beverages: tea (e.g., green, chinese), herbal teas, coffee
- Food supplements and health products
- Fats and oils
- Herbs and spices, food flavor ingredients
- Perfumes and scents
- Essential oils, others …



(http://www.sciencemag.org/cgi/content/full/285/5435/1853/F1)

(*Philippine Daily Inquirer* 06 June 2010 (Sunday), page A-19.)



On the Citizens' Right to Information

A Statement of Hope & Support from the Medical Profession

We are at a special juncture in our history as a nation when every citizen hopes that real change finally comes in governance, in our politics, and in the way we think as a people. The Medical Profession, represented here by the various Medical Societies and Associations listed below, is hopeful that in the desire to address the elements needed to rebuild our nation, everyone - government leaders, heads of corporations, the clergy, private citizens - would put the **HEALTH AND WELFARE OF THE FILIPINOS** above all other priorities.

The right to health is one of the fundamental rights enshrined in Article II of our 1987Constitution. Section 15 expressly declares, "the State shall protect and promote the right to health of the people and as a policy instill health consciousness among them".

The right to health includes the right to education and information. Access to information, including the right to seek, receive and impart information and ideas concerning health issues is considered an integral component of the right to health. We want every citizen to assume responsibility and accountability over his own health. Providing him the right information and education is the most important step in that direction. It is also the most cost-efficient.

As the Philippines embraces the lifestyle of the western world and exposes itself to the ravages of diseases that can otherwise be prevented by adequate information and proper education; and as the healthcare sector strives to improve its capacity to protect the public from ignorance, fear, mis-information, and the overwhelming power of the media, the State must pursue its mandate to inform and educate its citizens, and to protect them from deceptive, unfair and unconscionable sales acts and promotion practices.

The increasing prevalence of lifestyle diseases leading to heart attacks, heart failure, stroke, cancer, HIV infection and AIDS has reached alarming levels that require us to confront their causes without equivocation, and to institute prompt and aggressive interventions. To this end, the DOH under Secretary Esperanza I. Cabral has manifested strength of character and political will by signing AO 2010-0008 and AO 2010-0013 against the odds of fighting Big Business interests. We in the medical profession fully support her and will continue to support her as she takes on bigger tasks for the sake of our nation's health.

This is the kind of resolve we expect from our government servants; this is the kind of leadership we hope to see in the next government.

We fully support AO 2010-0008 signed by Dr. Cabral that provides the correct context and labeling of health and food supplements written in our national language. Health and food supplements are not medicines and should not be advertised as a cure for disease conditions. We have seen patients die of kidney and liver failure because of unregulated use of herbal concoctions; we see countless patients daily who replace their life-protecting medicines with these supplements – with unfortunate outcomes.

"Ang mga health and food supplements ay hindi gamot at hindi dapat gamiting panggamot sa anumang uri ng sakit."

the government can do well to prevent. It frustrates us no end when the solutions to our nation's health problems are right there in front of all of us, but our leaders opt to look the other way. Debates and TROs can go on and on; the truth about health and disease remains the same.

We need all the help we can get from our government leaders, the politicians, the clergy, and the businessmen in putting back the sense of right and wrong, the sense of urgency to deal with real priorities in nation-building, and the common sense of addressing our health problems simply and with a sense of duty.

Let us all work together to provide our citizens with the right information and the correct education. Nothing comes out of ignorance but illness and the inability to take care of oneself. We continue to hope for good governance, for the enlightenment of our leaders on the importance of health, and for the best health outcomes that secure the future of our country.

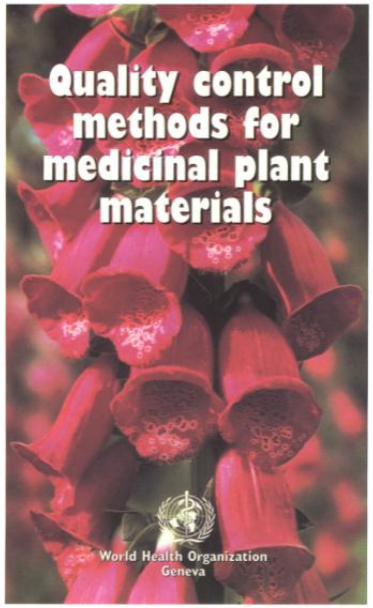
We support nothing less than real leadership.

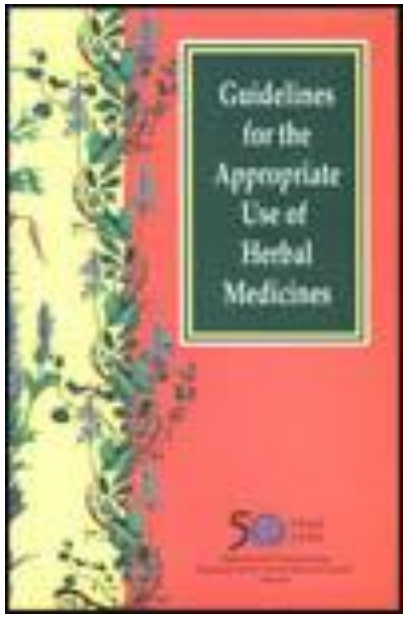
- The Philippine College of Physicians
- The Philippine Society of Gastroenterology
- The Diabetes Philippines
- The Philippine College of Chest Physicians
- The Philippine Society of Geriatric Medicine
- The Philippine Society of Hypertension
- The Philippine Heart Association
- The Philippine Society for Microbiology and Infectious Diseases
- The Philippine Lipid & Atherosclerosis Society
- The Philippine Rheumatology Association
- The Philippine Society of Medical Oncology
- The Philippine Society of Endocrinology and Metabolism
- The Philippine Society of Nephrology

(*Philippine Star* 06 June 2010 (Sunday), page B-9.)

Overview of Herbal Medicine Regulation in the World

- WHO recognizes the important and historical role of herbal medicine in health. Herbal medicine is a major form of treatment for more than 70% of the world's population.
- The *Guidelines for the Assessment of Herbal Medicines* states that a substance's historical use is a valid way to document safety and efficacy in the absence of scientific evidence to the contrary.
- Appropriate use
- Quality control methods
- Recommended labeling





http://www.holisticonline.com/Herbal-Med/hol_herbalmed-drugreg.htm

Overview of Herbal Medicine Regulation in the World

- EU follows the "doctrine of reasonable certainty" and is generally consistent with WHO.
  - France: traditional medicines can be sold with labeling based on traditional use
  - Germany considers active ingredient of herbal product and standardization (Commission E).
  - England generally follows the rule of prior use

http://www.holisticonline.com/Herbal-Med/hol_herbalmed-drugreg.htm

Overview of Herbal Medicine Regulation in the World

- USA: herbal products can be marketed only as food supplements. Herbal products can make no specific health claims without FDA approval.
- Asia: use of patent herbal remedies composed of dried and powdered whole herbs or herb extracts, also in tablet form
  - China: wide-spread use of traditional herbals
  - Japan: Kampo medicine is derived from Chinese medicine
  - India: Ayurvedic medicine

http://www.holisticonline.com/Herbal-Med/hol_herbalmed-drugreg.htm

Recommended Labeling Requirements for Herbal Medicine

(a) name of product;

(b) name and quantity (in dry weight when relevant) of active ingredient(s);

(c) dosage form;

(d) directions for use including indications, dosage, mode of administration, duration of use, age group limitations, and use during pregnancy and lactation;

(e) warning statements and relevant contraindications, adverse effects, if any, and overdose information when relevant;

(f) batch number;

(g) expiry date;

(h) storage conditions;

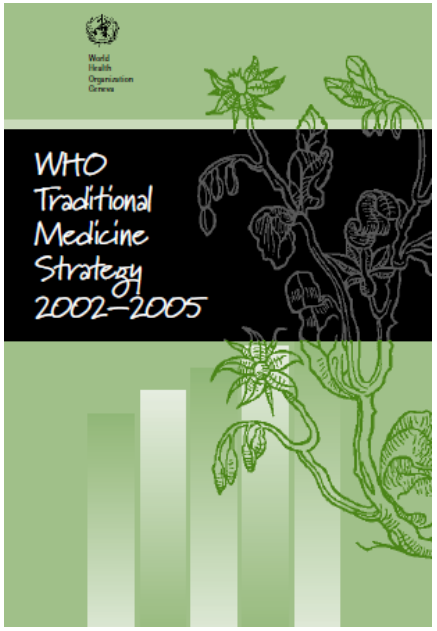
(i) name and address of manufacturers and/or importers; and

(j) registration or notification (listing) number.

(Guidelines for the Appropriate use of Herbal Medicines, 1998, WHO)

The Changing Landscape of Herbal Medicine, Food and Wellness

Traditional Medicine "is a comprehensive term used to refer both to TM systems, such as traditional Chinese medicine, Indian ayurveda and Arabic unani medicine, and to various forms of indigenous medicine. TM therapies include **medication therapies** — if they involve use of herbal medicines, animal parts and/or minerals — and **nonmedication therapies**… such as acupuncture, and manual and spiritual therapies.



"In countries where the dominant health care system is based on allopathic medicine, or where TM has not been incorporated into the national health care system, TM is often termed "**complementary**", "**alternative**" or "**non-conventional**" medicine." (eg, US FDA: Complementary and Alternative Medicine)

The Changing Landscape of Herbal Medicine, Food and Wellness

- **Herbal Medicine**: Makes therapeutic claim; includes crude herbal materials, preparations and finished products, that contain as active ingredients, parts of plants or combinations thereof. (WHO Traditional Medicine Strategy 2002-2005). In Europe, also called "phytotherapy".
- Dietary Supplement
- Nutriceutical
- Functional Food

The Changing Landscape of Herbal Medicine, Food and Wellness

- Herbal Medicine
- **Dietary Supplement**: A product that is intended to supplement the diet and that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, herb or other botanical material, an amino acid, a dietary substance to supplement the diet by increasing the total daily intake. (US Dietary Supplement Health and Education Act, 1994). Philippine FDA uses a very similar definition.
- Nutriceutical
- Functional Food

The Changing Landscape of Herbal Medicine, Food and Wellness

- Herbal Medicine
- Dietary Supplement
- **Nutriceutical**: Term coined by Stephen DeFelice in 1989 from "Nutrition" and "Pharmaceutical". Zeisel (Science 1999): Nutraceuticals are dietary supplements administered in large dosages in order to obtain pharmacological effects. Nutraceuticals deliver a concentrated orm of a presumed bioactive agent from food, presented in a non-food matrix, in dosages that exceed those that can be obtained in normal food.
- Functional Food

The Changing Landscape of Herbal Medicine, Food and Wellness

- Herbal Medicine
- Dietary Supplement
- Nutriceutical
- **Functional Food**: A food that is consumed as part of a normal diet and which is claimed to have health-promoting or disease-preventing properties beyond the basic function of supplying nutrients. Examples include probiotics (fermented foods with live cultures), prebiotics (e.g., inulin). This term was first used in Japan in the 1980s where there is a government approval process for functional foods called Foods for Specified Health Use (FOSHU).

The Changing Landscape of Herbal Medicine, Food and Wellness

- **Herbal Medicine**
- **Dietary Supplement**
- **Nutriceutical**
- **Functional Food**

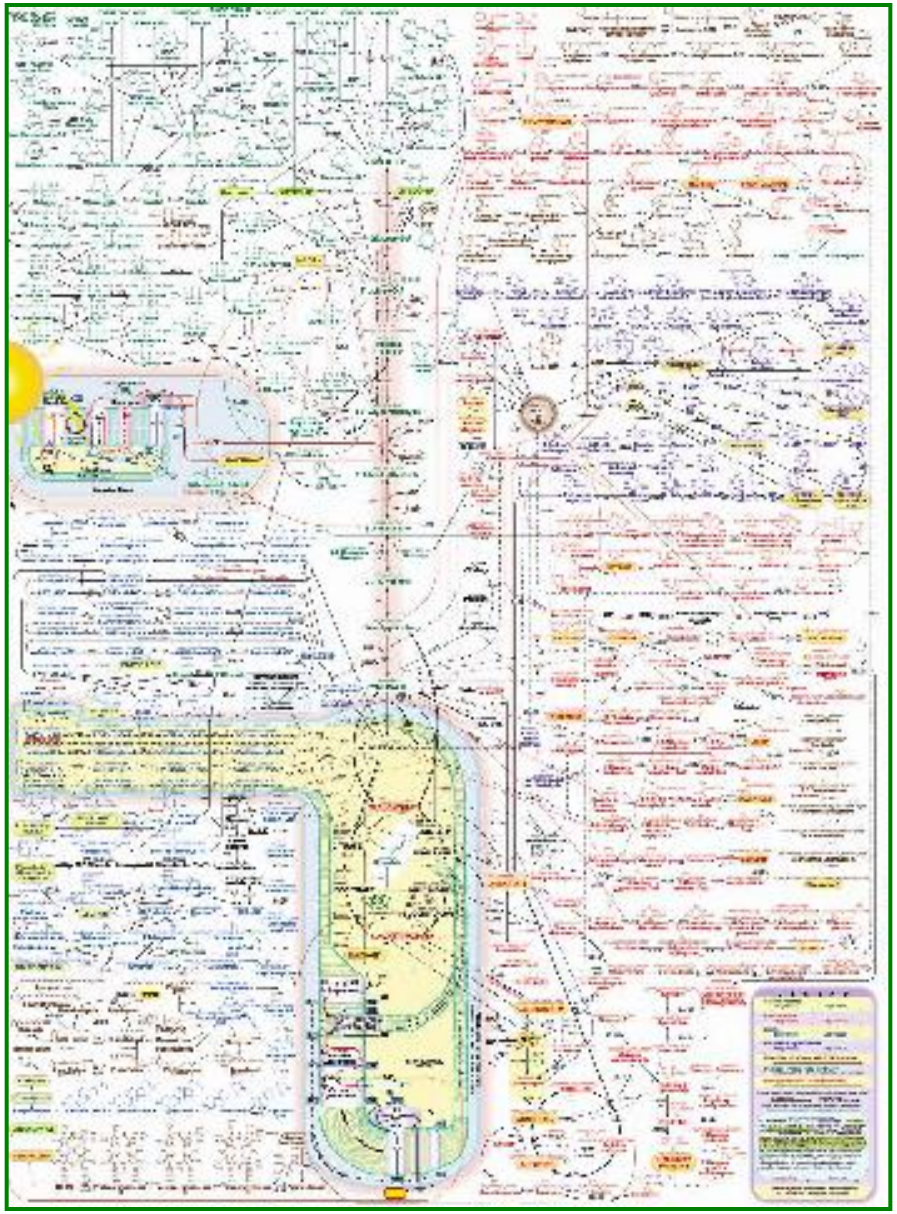
☑ Natural Products Chemistry is key to all of these!

The study of natural products is multidisciplinary

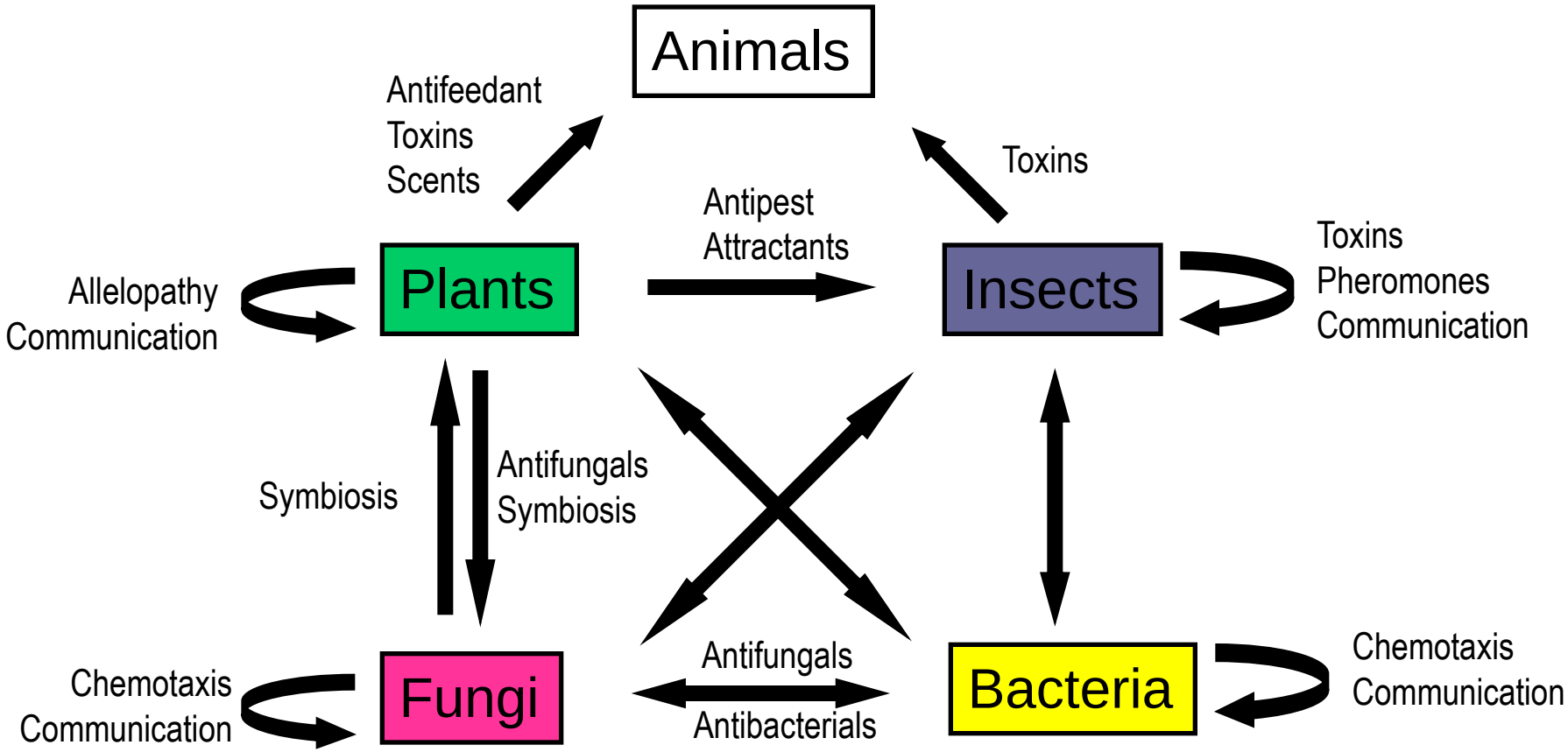
Biology ← → **Chemistry**
Taxonomy . Botany
Organic synthesis
Agriculture . Pharmacology . Pharmaceutical Science . Organic analytical chemistry
Entomology . Microbiology . Biotechnology/Molecular Biology . Biochemistry
Genomics . Proteomics
Metabolonomics

Metabonomics offers the opportunity to find patterns of changes in the entire metabolism.

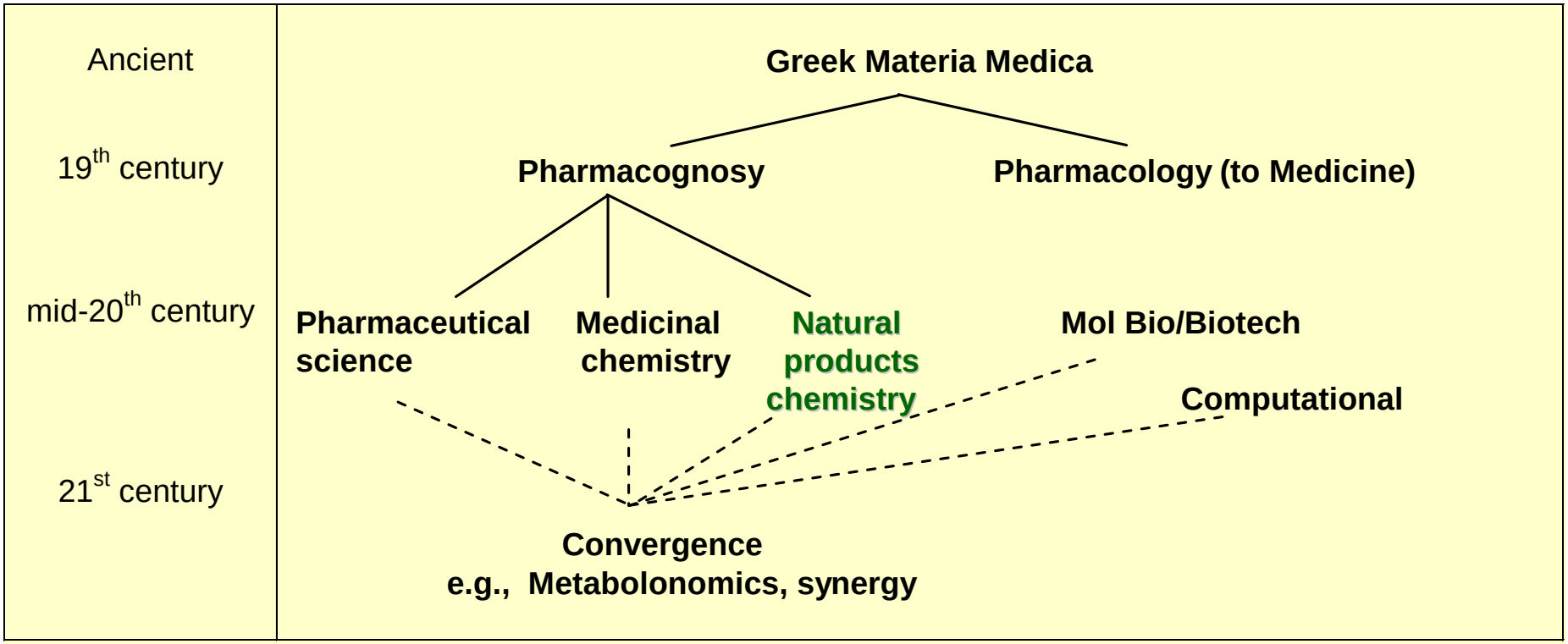
(Donald Nicholson, ©International Union of Biochemistry & Molecular Biology http://pubs.acs.org/cen)



Natural products and Ecology



A brief history of natural products chemistry



Techniques used in natural products chemistry

1800	1850	1900	1950	1975	2000
Type of research undertaken:					
Isolation, characterization					
	Pharmacognosy & Pharmacology				
		Organic synthesis			
		Chromatography	Spectroscopy		
			Biogenetic studies		
				Biochemistry; Enzymology	
					Molecular Biology
					Metabolonomics
Techniques used:					
basic physico-chemical measurements					
		TLC	column chrom	GC	HPLC / Electrophoresis
			X-ray	UV-vis IR	MS / NMR
			Radioisotopes		
			Enzymes		Computational methods
					Tissue culture
					Mol Bio / Biotech
					Combinatorial chem

Modern directions in natural products chemistry:

- Genomics of bacteria and plants
- Novel and efficient synthetic methods
- Genetic engineering of bacteria and plants
- Enzyme synthesis
- Computational methods and modeling
- High efficiency chromatography
- Spectroscopic methods
- High-throughput screening
- Synergism
- Biotransformation

Natural Products as Sources of New Drugs

(Ref: Newman, Cragg, and Snader, "Natural Products as Sources of New Drugs over the Period 1981-2002," *J. Nat. Prod.* **2003,** *66,* 1022-1037)

Natural products remain an important source of new structures, though not the final drug entity.

Indication	Total drugs	B	N	ND	S	SN	V
antibacterial	90		9	61	19	1	
anticancer	79	12	9	21	25	10	2
antiinflammatory	50	1		13		36	
TOTAL	868	91	40	209	386	131	11
Proportion	100%	10.5	4.6	24.0	44.5	15.0	1.2

B: biologicals (peptides); **N**: nat prod extract; **ND**: semi-synthetic starting from nat prod; **S**: totally synthetic using random screening ; **SN**: totally synthetic but based on nat prod; **V**: vaccine

Although the combinatorial strategy has succeeded as a method of optimizing structures, there is still no *de novo* combinatorial compound that has made it to drug product.

Natural Products as Sources of New Drugs

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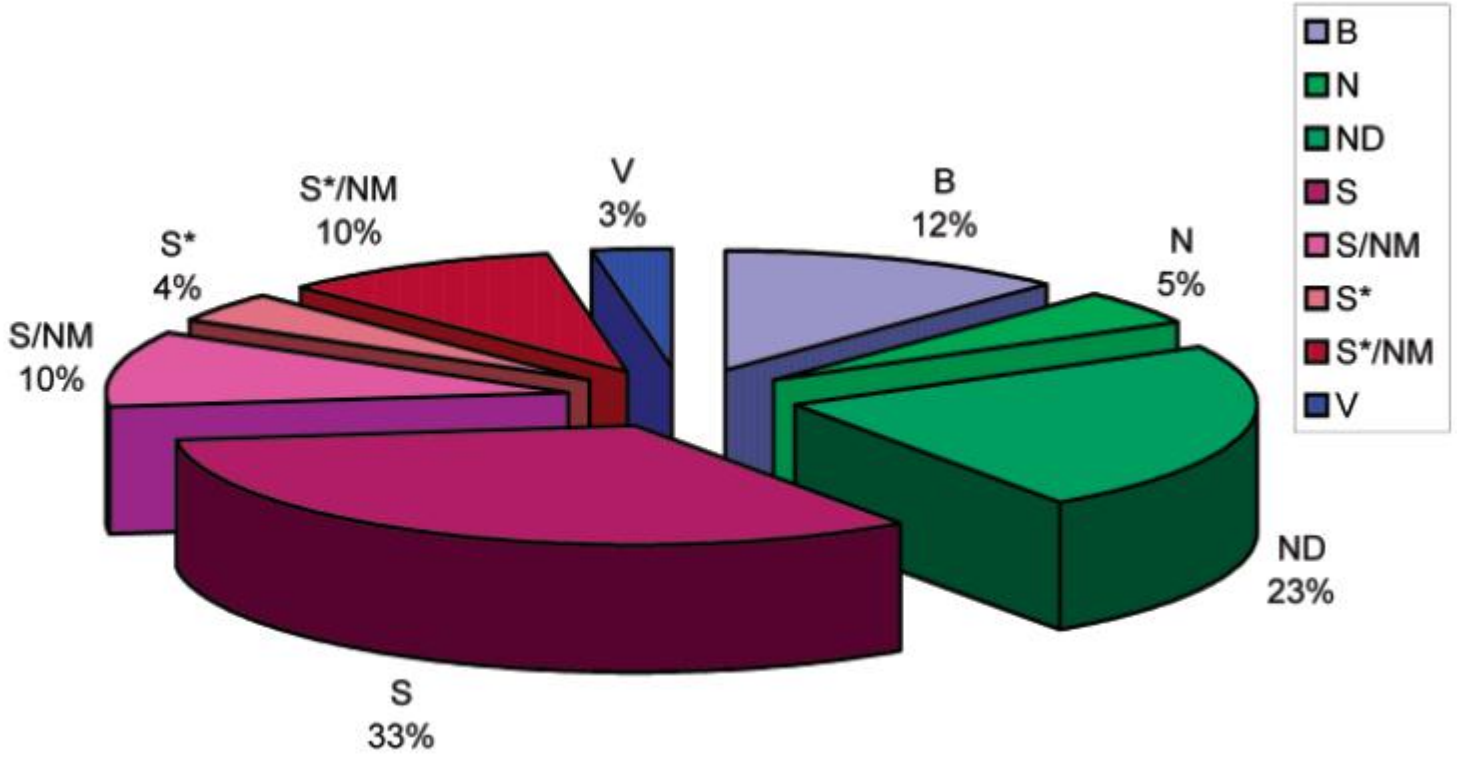
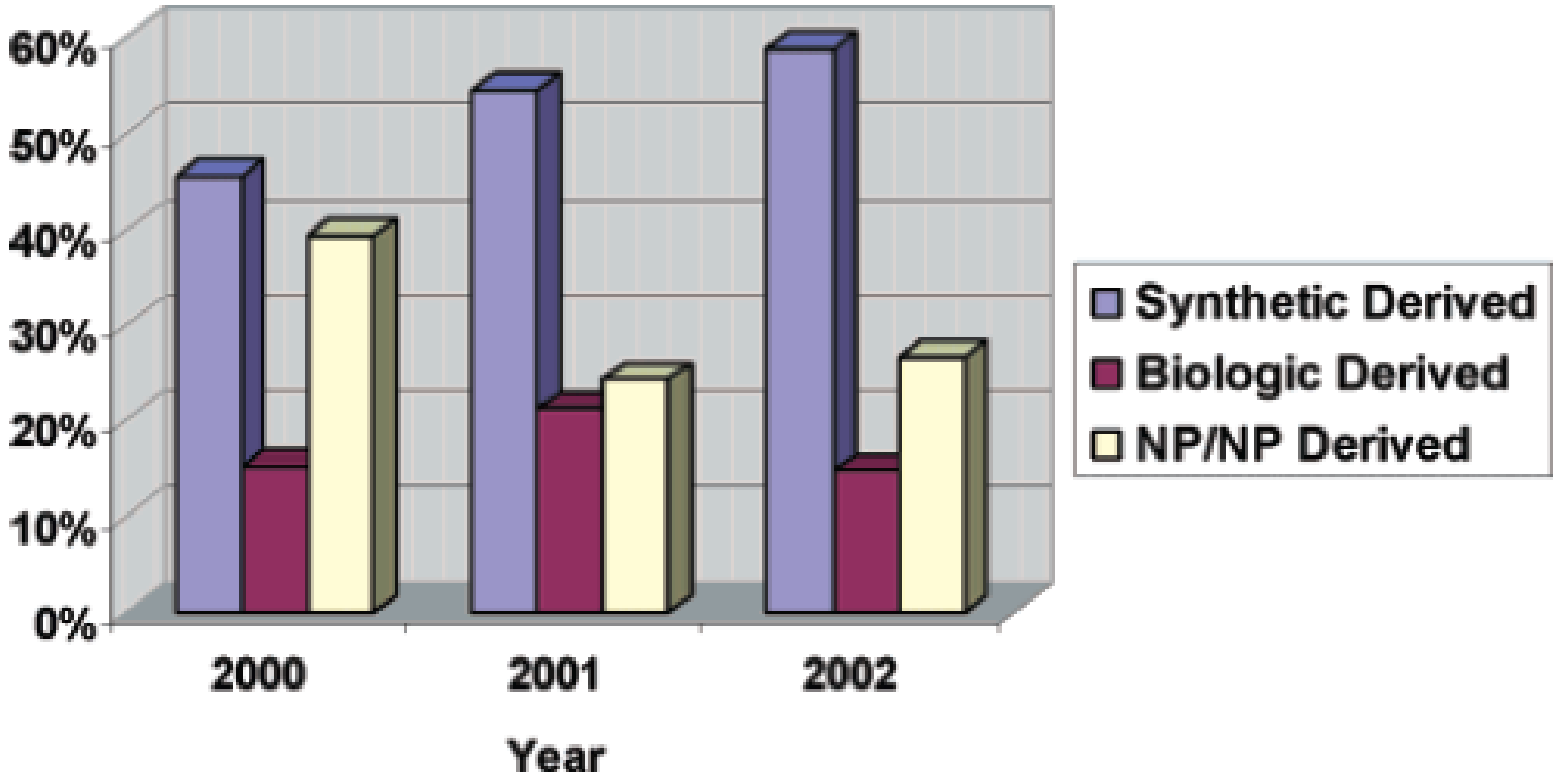
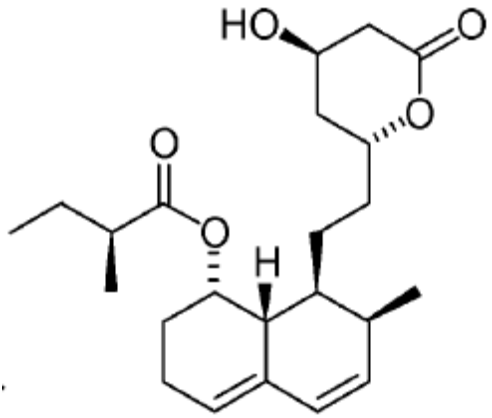


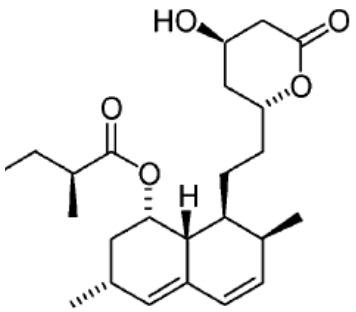
Figure 1. All new chemical entities, 1981−2002, by source ($N = 1031$).

Natural Products as Sources of New Drugs

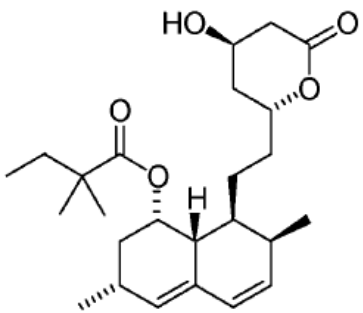
(Ref: Mark Butler, "The Role of Natural Product Chemistry in Drug Discovery," *J. Nat. Prod.* **2004,** *67*, 2141-2153)



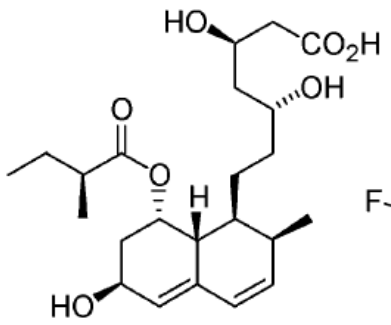




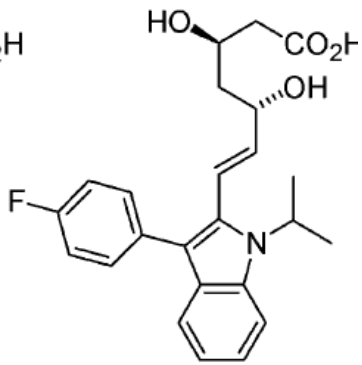
Lovastatin (15)
(Mevacor®)



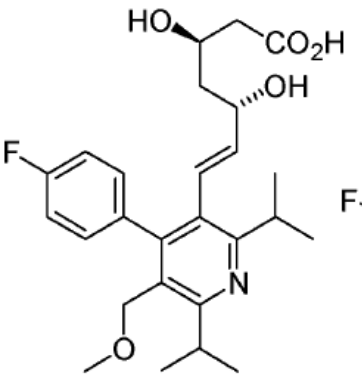
Simvastatin
(Zocor®)



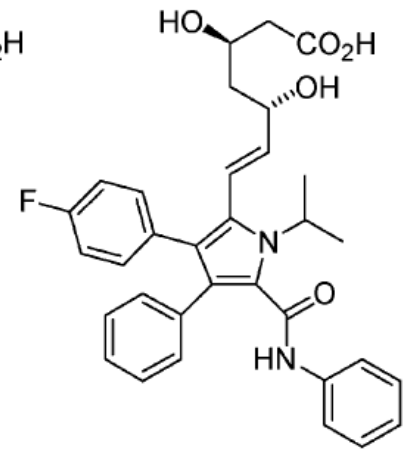
Pravastatin
(Pravachol®)



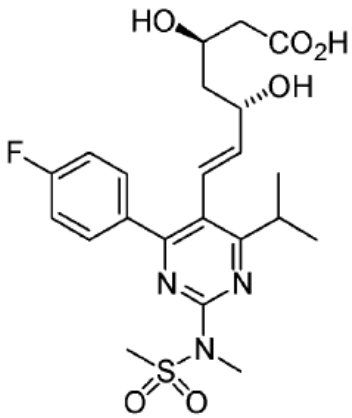
Fluvastatin
(Lescol®)



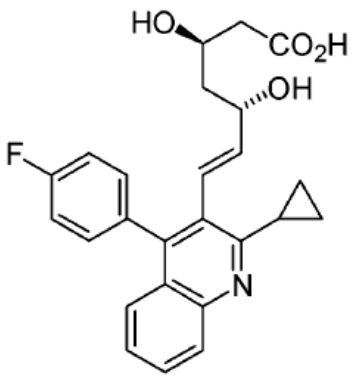
Cerivastatin
(Baycol®)
Note: removed from market



Atorvastatin
(Lipitor®)

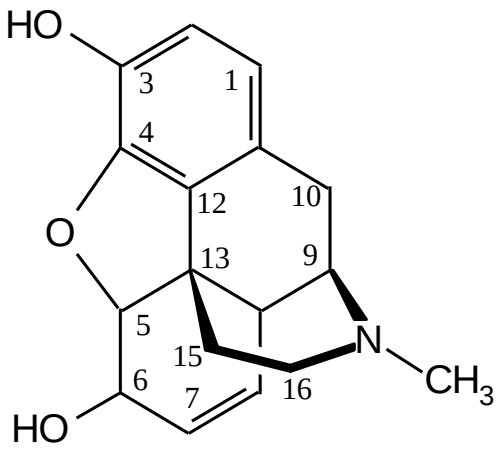


Rosuvastatin (36)
(Crestor®)



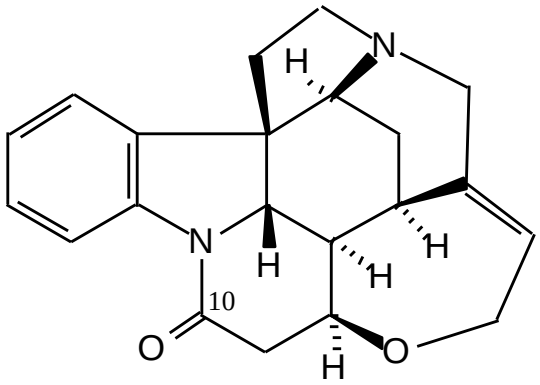
Pitavastatin (37)
(Livalo®)

Some milestones in natural products chemistry:



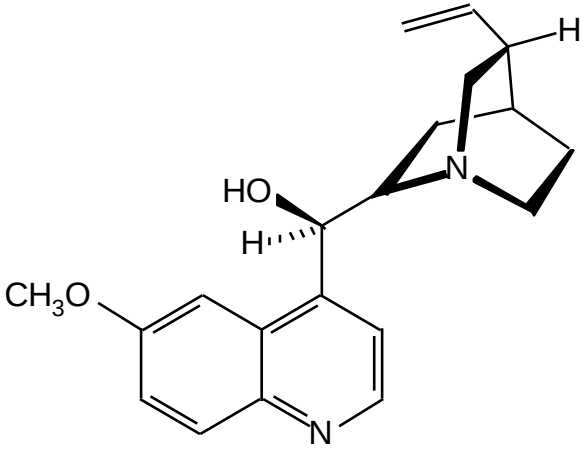
Morphine
(aromatic alkaloid from opium, *Papaver somniferum*)

Isolation: 1806, Sertürner
Structure: 1925, Robinson
Synthesis: 1954, Ginsberg
Biogenesis: 1959, Leete



Strychnine
(aromatic alkaloid from *Strychnos nux-vomica*)

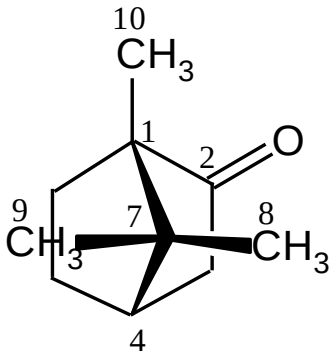
Isolation: 1818, Pelletier & Caventou
Structure: 1946, Robinson
Synthesis: 1954, Woodward
2001, Eichberg



Quinine
(quinoline alkaloid from *Cinchona* species)

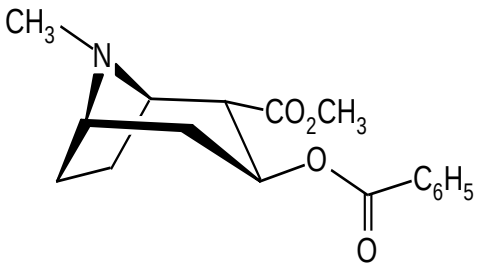
Isolation: 1820, Pelletier & Caventou
Synthesis: 1944, Woodward

Some milestones in natural products chemistry:



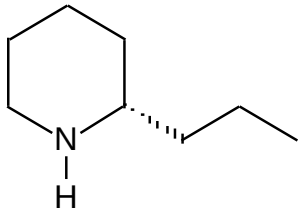
Camphor
(monoterpene from *Cinamomum camphora*)

Isolation: 1845, Bouchardat



Cocaine
(aliphatic alkaloid from *Erythroxylon coca*)

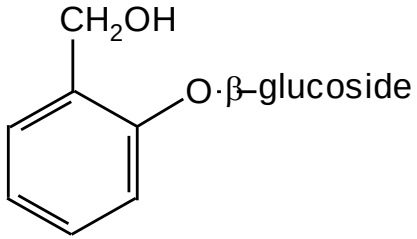
Isolation: 1859, Niemann
Synthesis: 1923: Willstätter



Coniine
(aliphatic alkaloid from hemlock, *Conium maculatum*)

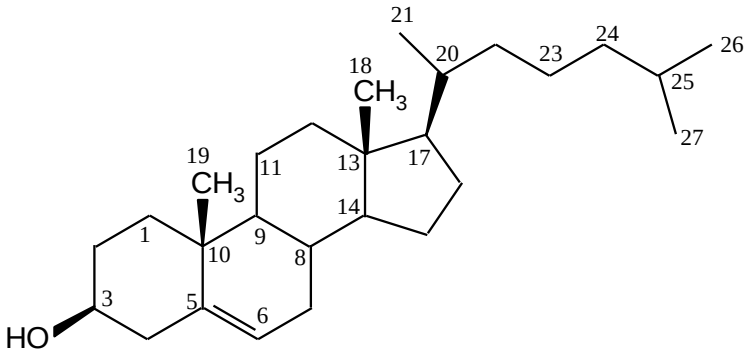
Isolation: 1886, Ladenburg
Structure: 1926, Koller

Some milestones in natural products chemistry:



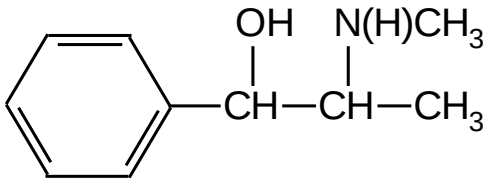
Salicin
(aromatic alcohol from *Salix* species)

Structure and synthesis:
1906, Irvine



Cholesterol
(steroid from gallstones)

Isolation: 1909, Windaus
Structure: 1932, Wieland
Synthesis: 1964, Johnson
Biogenesis: 1966, Cornforth



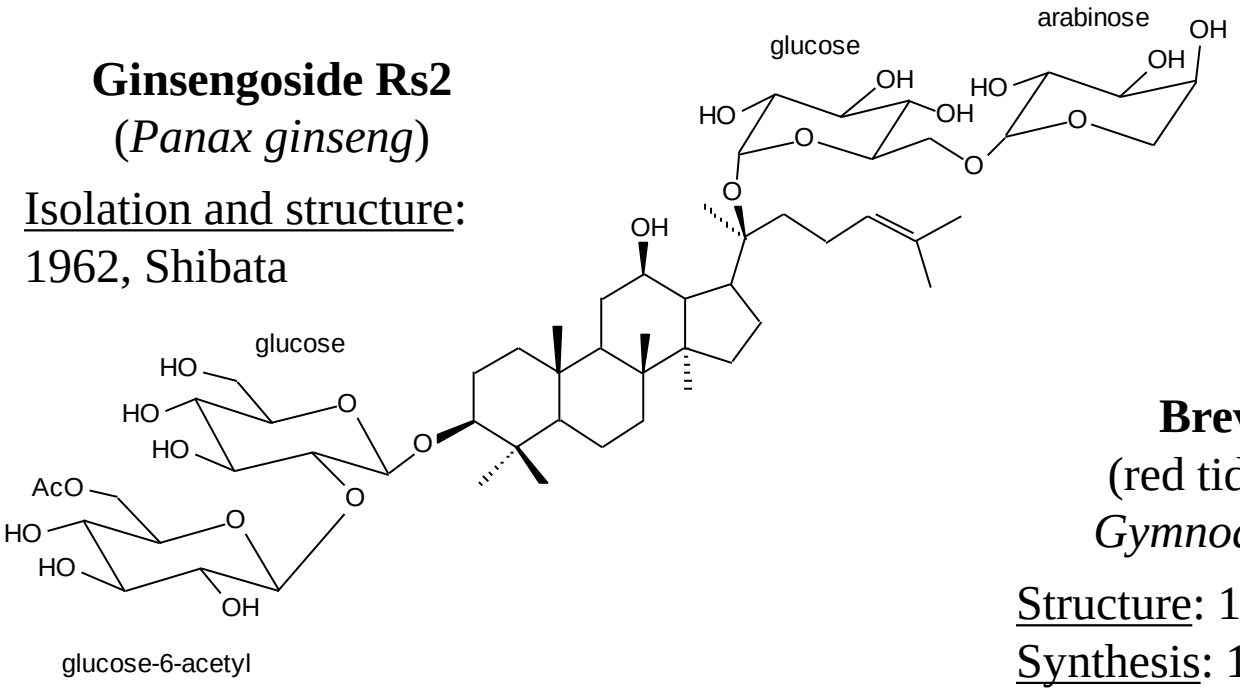
Ephedrin
(aromatic alkaloid from *Ephedra equisetrina and E. sinica;* "ma huang")

Structure and synthesis:
1920, Späth and Göring

Some milestones in natural products chemistry:

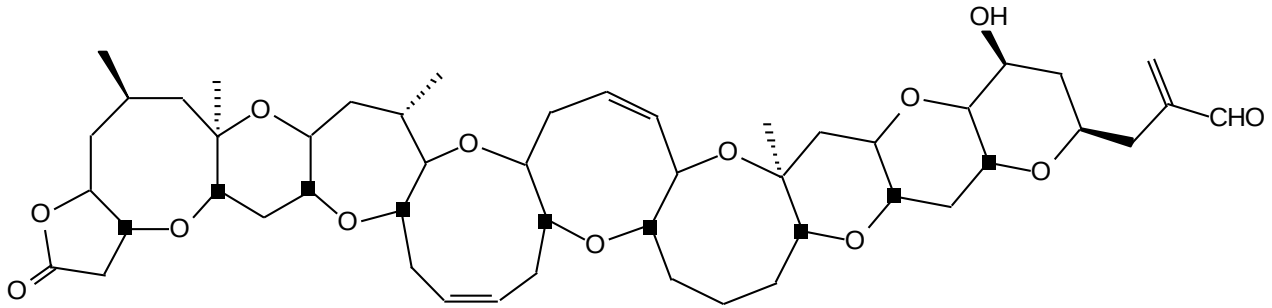
Ginsengoside Rs2
(*Panax ginseng*)

Isolation and structure:
1962, Shibata

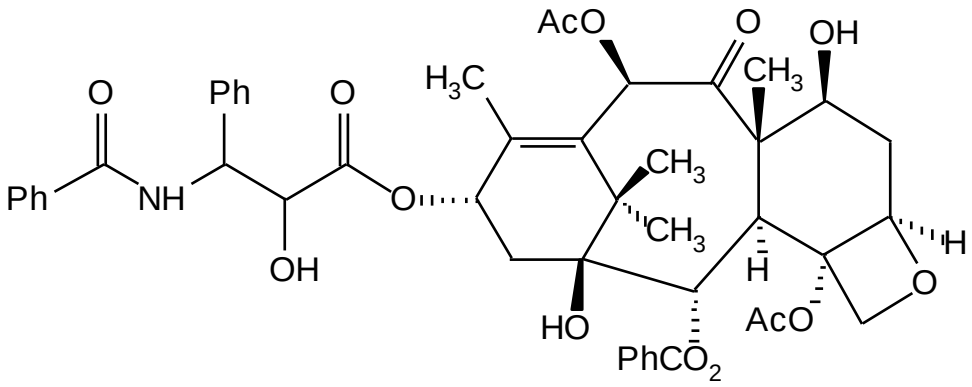


Brevetoxin-A
(red tide toxin from
Gymnodinium breve)

Structure: 1986, Clardy
Synthesis: 1987, Nakanishi

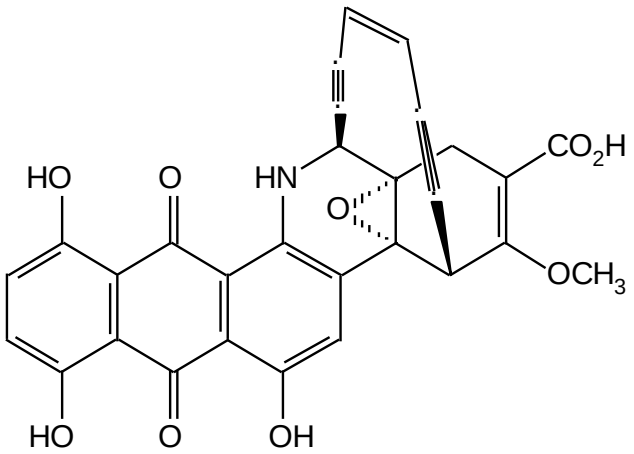


Some milestones in natural products chemistry:



Taxol
(antitumor diterpene from
Pacific yew, *Taxus* species)

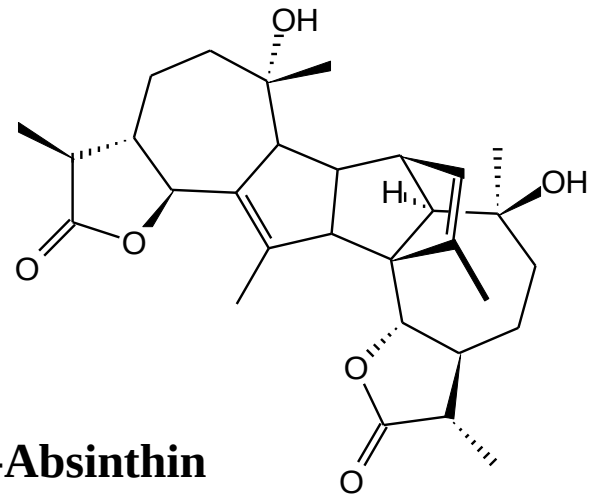
Isolation: 1971, Wani *et al*.
Structure: 1971, Wani *et al*.



Dynemicin A
(antibiotic polyketide from
Micromonospora chersina)

Structure: 1989, Matsumoto and Clardy
Synthesis: 1991, Nicolau
Biosynthesis: 1992, Tokiwa *et al*.

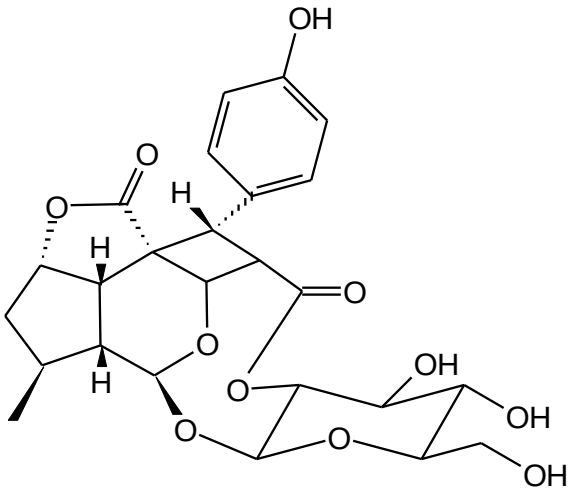
Some milestones in natural products chemistry:



(+)-Absinthin

(dimeric diterpene from *Artemisia absinthium* L., an anthelmintic)

Isolation: 1953, Herout
Structure: NMR: 1980, Beauharie, X-ray: 1985, Karimov
Synthesis: 2004, Zhang



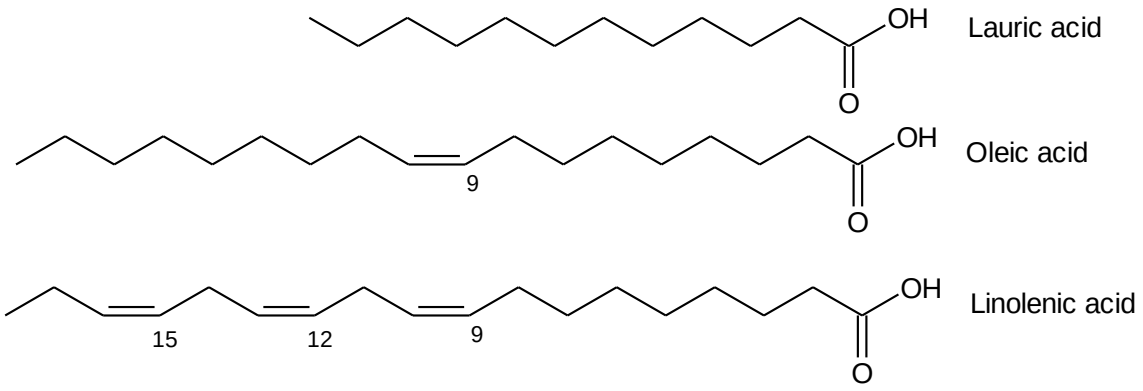
(-)-Littoralisone

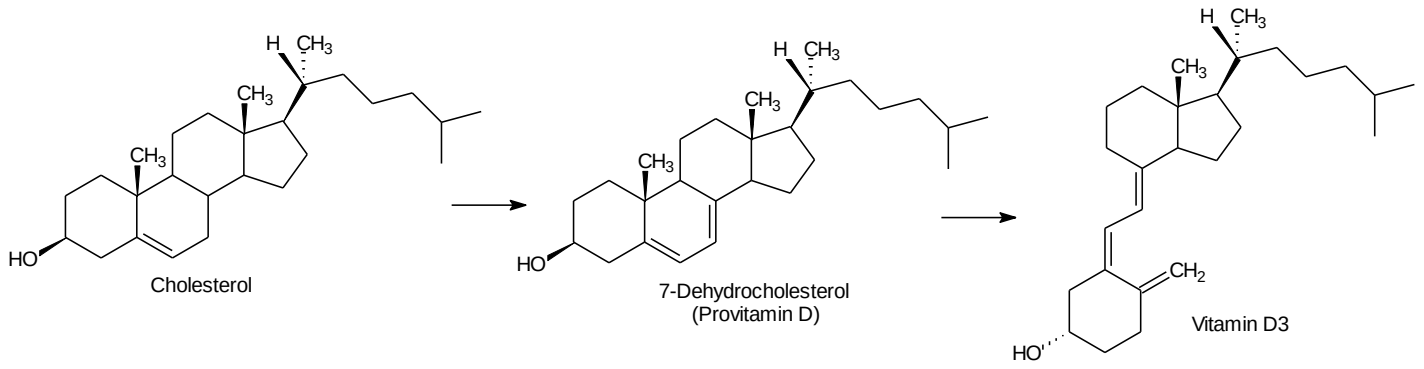
(neurotrophic growth factor, iridoid from *Verbena littoralis* L.)

Isolation and structure: 2001, Li
Synthesis: 2005, Mangion

Some milestones in natural products chemistry:

Some recent rediscoveries:

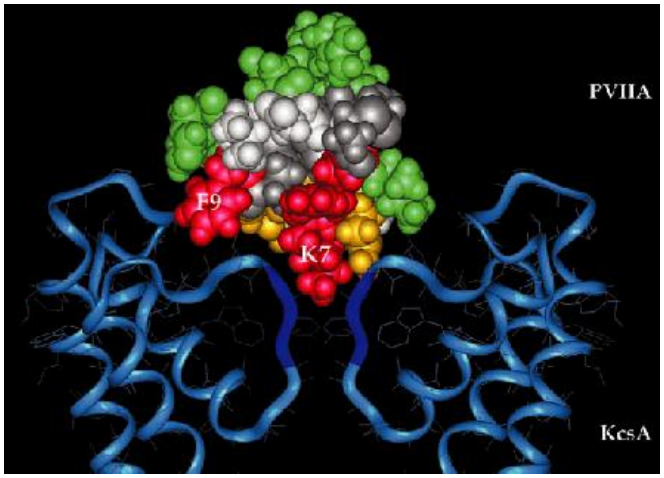




Some milestones in natural products chemistry:

TABLE 1. *Conopeptides targeted to Na channels* (Terlau and Olivera, *Physiol.Rev.*, 84: 41–68, 2004)

Peptide	*Conus* Species	Subtype Targeted	Sequence
μ-Conotoxins			
μ-GIIIA	*C. geographus*	Muscle	RDCCTOOKKCKDRQCKOQRCCA*
μ-GIIIB	*C. geographus*	Muscle	RDCCTOORKCKDRRCKOMKCCA*
μ-PIIIA	*C. purpurascens*	Diverse	ZRLCCGFOKSCRSRQCKOHRCC*
μ-SmIIIA	*C. stercusmuscarum*	TTX sensitive TTX insensitive (amphibian)	ZRCCNGRRGCSSRWCRDHSRCC*
μO-Conotoxins			
μO-MrVIA	*C. marmoreus*	(Diverse)	ACRKKWEYCIVPIIGFIYCCPGLICGPFVCV
μO-MrVIB	*C. marmoreus*	(Diverse)	ACSKKWEYCIVPILGFVYCCPGLICGPFVCV
δ-Conotoxins			
δ-PVIA	*C. purpurascens*	(Diverse)	EACYAOGTFCGIKOGLCCSEFCLPGVCFG
δ-SVIE	*C. striatus*	(Not established)	DGCSSGGTFCGIHOGLCCSEFCFLWCITFID
δ-TxVIA	*C. textile*	(Molluscan subtype)	WCKQSGEMCNLLDQNCCDGYCIVLVCT
δ-GmVIA	*C. gloriamaris*	(Not established)	VKPCRKEGQLCDPIFQNCCRGWNCVLFCV



Isolation and Structure: Olivera and Cruz and co-workers, 1984 onwards

FIG. 3. Hypothetical docking orientation of κ-conotoxin PVIIA on the outer vestibule of the KcsA K channel pore. The two marked residues of the peptide, K7 and F9, comprise a dyad motif that is a general feature of polypeptidic toxins targeted to K channels. All residues colored red are major determinants of binding affinity, yellow residues make a measurable contribution, and green residues do not directly interact with the K channel blocked by κ-PVIIA. The *Shaker* K channel sequences have been overlaid on the KcsA crystal structure determined by McKinnon and co-workers (shown in blue)

The development of methods in organic chemistry is linked to developments in natural products chemistry:

1800s

- Development of techniques in organic chemistry
- Wagner-Meerwein rearrangement in monoterpenes

early 1900s

- The early work on alicyclic chemistry was done on steroids

1950~1980

- Steric control of chemical reactions, e.g., borneol, steroids
- Studies by UV-visible spectroscopy (e.g., Vitamin A)
- Development of NMR (2-D NMR, NOE)

1980 ~ present

- Recent synthetic methodologies
- Enzyme-mediated synthesis, cell culture, genetics and biotechnology

The development of synthetic organic chemistry is linked to natural products chemistry:

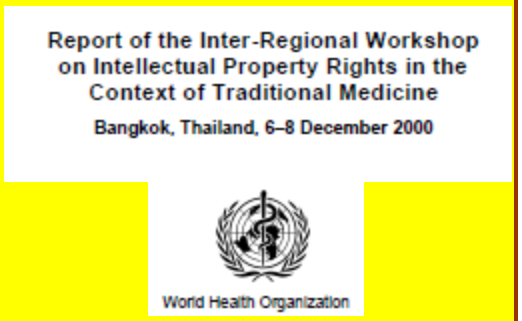
- Robert Robinson, Nobel Prize in Chemistry in 1947: structure of steroid hormones and alkaloids, in particular, strychnine.
- Robert B Woodward, Nobel Prize in Chemistry in 1965: strychnine, lysergic acid and lanosterol: 1954; chlorophyll and tetracycline: 1960; quinine, patulin, cholesterol and cortisone: 1965.
- Elias J. Corey, Nobel Prize in Chemistry in 1991
- Koji Nakanishi-brevetoxin A, 1987
- K.C. Nicolau-dynemicin A, 1991.

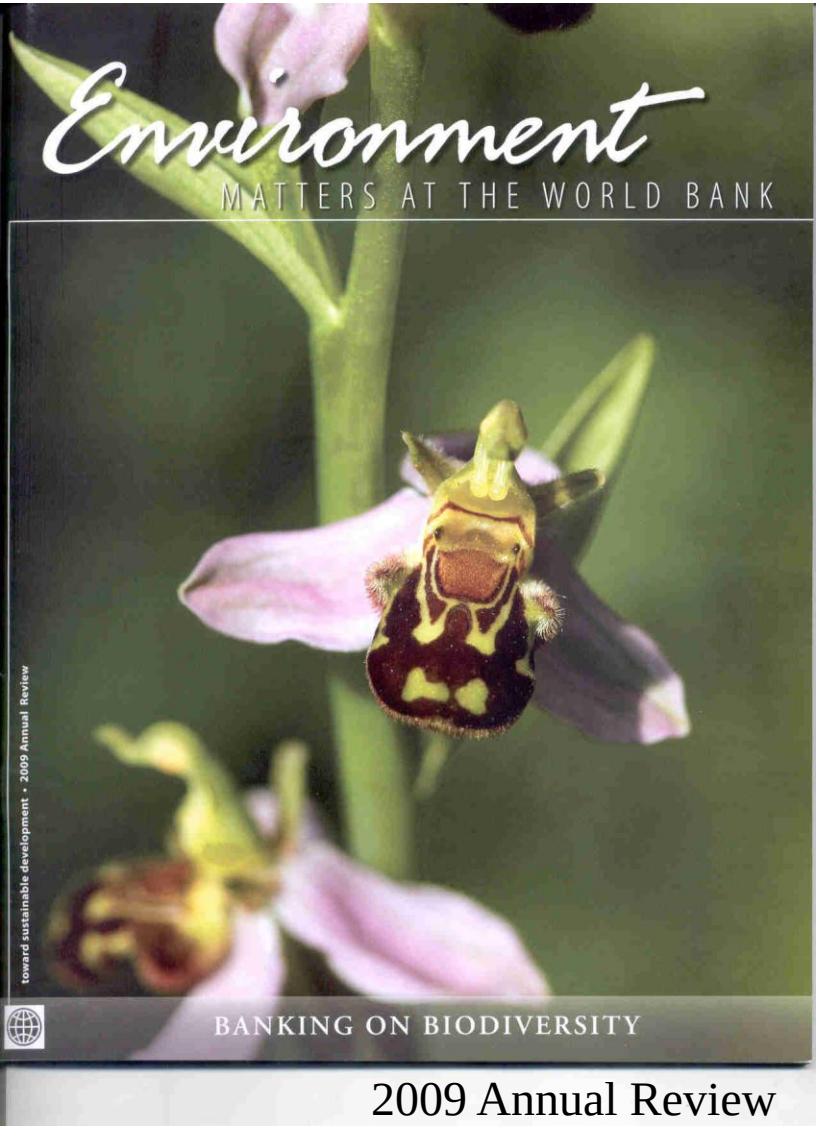
The role of the study of natural products today

- Nature still holds many secrets which we can learn from: chemical structure, biosynthesis, the role and relationship of plants to other organisms.
- The study of natural products merges science with culture.
- For countries which harbor rich biodiversity, the study of natural products is an important way of developing one's natural resources.
- Natural products should use the new developments, e.g., molecular biology, computational science.

Issues and challenges in Natural Products today

1. Loss of biodiversity
2. Intellectual Property Rights
   - Patent protection (pharma companies)
   - Biopiracy (source countries)
3. Western drugs:
   a. High cost of drug development
   b. New drug leads and targets
4. Herbal products:
   a. Regulation
   b. Improvement in quality
   c. Elucidation of mechanism of action





2009 Annual Review

VIEWPOINTS

Sustainable Drugs and Global Health Care

(Ref: Geoffrey A. Cordell, *Quim. Nova*, Vol. 32, No. 5, 1356-1364, 2009)

Each day, Earth's finite resources are being depleted for energy, for material goods, for transportation, for housing, and for drugs. As we evolve scientifically and technologically, and as the population of the world rapidly approaches 7 billion and beyond, among the many issues with which we are faced is the continued availability of drugs for future global health care. Medicinal agents are primarily derived from two sources, synthetic and natural, or in some cases, as semi-synthetic compounds, a mixture of the two. For the developed world, efforts have been initiated to make drug production "greener", with milder reagents, shorter reaction times, and more efficient processing, thereby using less energy, and reactions which are more atom efficient, and generate fewer by-products. However, most of the world's population uses plants, in either crude or extract form, for their primary health care. There is relatively little discussion as yet, about the long term effects of the current, non-sustainable harvesting methods for medicinal plants from the wild, which are depleting these critical resources without concurrent initiatives to commercialize their cultivation. To meet future public health care needs, a paradigm shift is required in order to adopt new approaches using contemporary technology which will result in drugs being regarded as a sustainable commodity, irrespective of their source. In this presentation, several approaches to enhancing and sustaining the availability of drugs, both synthetic and natural, will be discussed, including the use of vegetables as chemical reagents, and the deployment of integrated strategies involving information systems, biotechnology, nanotechnology, and detection techniques for the development of medicinal plants with enhanced levels of bioactive agents.

Research areas in natural products today

1. Structural elucidation (speed of analysis, sample throughput complexity of structures)
2. Metabolonomics
3. Synergy and biotransformation
4. Biosynthesis
5. Biological activity
    a. Ecological
    b. Pharmaceutical properties / drug discovery
    c. Healthcare and cosmetic products
6. Molecular biology and Biotechnology
7. Quantitative natural products chemistry

Natural products chemistry is at the intersection of many fields: