Brazilian biodiversity as a source of new drugs

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International Workshop on metabolomics in the context of systems biology: a rational approach to search for lead molecules from nature.

São Paulo, 24-25 February Brazil

Exenatide (INN, marketed as Byetta) is one of a new class of medications (incretin mimetics) approved (Apr 2005) for the treatment of diabetes mellitus type 2.

*Heloderma suspectum* (Helodermatidae) 39-amino-acid peptide

The Cone snail and the development of Prialt®

Sirolimus (INN) is a relatively new immunosuppressant drug used to prevent rejection in organ transplantation, and is especially useful in kidney transplants.
Tiotropium bromide an anticholinergic drug for the treatment of chronic obstructive pulmonary disease


Atropa belladonna L., Solonaceae
Reconsidering natural products
Contemporary methodological approaches in the search for new lead compounds from higher plants.
Find a Needle in the Haytack
The discovery of Brazil

Brazil was first "discovered" by Europeans On April 22, 1500.

Pedro Álvares Cabral (c.1467-c.1520)
The early explorers
The Captivity of Hans Staden of Hesse, in A.D. 1547-1555, Among the Wild Tribes of Eastern Brazil in Marburg in 1557.
The origin of the name “Brazil”

Brazilwood: *Caesalpinia echinata* Lam. (Leguminosiae)  
The source of a perfect red dye

Brazilwood: *Caesalpinia echinata* Lam. (Leguminoseae)

“the discovery of brazilwood pigment”

Sir Robert Robinson
The Nobel Prize in Chemistry 1947

Brazil has 1/5 of the world biodiversity, with 50,000 species of plants, 5,000 of vertebrates, 10-15 millions of insects, and millions of microorganisms.
Brazilian’s Ecosystems
The Cerrado region of Brazil, comprising 21 percent of the country, is the most extensive woodland-savanna in South America. With a pronounced dry season, it supports a unique array of drought- and fire-adapted plant species and surprising numbers of endemic bird species. Large mammals such as the giant anteater, giant armadillo, jaguar and maned wolf also still survive here but are competing with the rapid expansion of Brazil's agricultural frontier, which focuses primarily on soy and corn. Ranching is another major threat to the region, as it produces almost 40 million cattle a year.

VITAL SIGNS

<table>
<thead>
<tr>
<th>Endemic Plant Species</th>
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<tr>
<td>Endemic Threatened Birds</td>
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<td>Endemic Threatened Mammals</td>
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<td>Endemic Threatened Amphibians</td>
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</table>

Extinct Species† | 0

© Cary Vynne
Vegetation typical of riverine ecosystems in the Cerrado.
Pilocarpine from *Pilocarpus ssp.* (Rutaceae)

The pilocarpine model of epilepsy

Cavalheiro E.A.
Neurologia Experimental, Escola Paulista de Medicina, São Paulo, Brasil

The systemic administration of a potent muscarinic agonist pilocarpine in rats promotes sequential behavioural and electrographic changes that can be divided in three distinct periods: (a) an acute period that built up progressively into a limbic status epilepticus and that lasts 24 h, (b) a silent period with a progressive normalization of EEG and behaviour which varies from 4 to 44 days, and (c) a chronic period with spontaneous recurrent seizures (SRSs). The main features of the SRSs observed during the long-term period resemble those of human complex partial seizures and recurs 2-3 times per week per animal. Therefore, this novel and unique experimental approach may serve as a model of epilepsy mimicking the human condition.

Key Words: pilocarpine — status epilepticus — limbic epilepsy, rats.
«The introduction of tubocurarine into anaesthetic practice, by Griffith and Johnson, in 1942, caused profound changes in the efficacy and safety of anaesthesiology»
"the most fruitful basis for the discovery of a new drug is to start with an old drug".

Prof. James W. Black
Nobel Price of medicine in 1988
Atracurium a synthetic derivative based in the structure of Tubocurarin

Bothrops jararaca snake and captropril development

Angiotensin-converting enzyme inhibitor

Captopril®

Enalopril®

BPP5

Prof. Sergio Henrique Ferreira
The stevioside from *Stevia rebaudiana* Bertoni (Asteraceae)

- 250–300 times sweeter than sucrose
- Heat stable, pH stable, and non-fermentable.

Crammer, B, and Ikan, R (1986) Sweet glycosides from the stevia plant. Chemistry in Britain 22: 915-916
Drink wars’ new flavor

Pepsi, Coke look to natural sweetener in marketing push

BY BETSY MCKAY

A little more than a year after Coca-Cola Co. disclosed the development of a natural sweetener it said might start a new generation of calorie-free drinks, PepsiCo Inc. claims it has beaten Coke to the punch.

Pepsi plans to introduce an enhanced-water drink within the next few weeks that contains a sweetener very similar to the one Coke has. Both sweeteners are derived from a promising but controversial herb called stevia. Neither has been approved by the Food and Drug Administration for use in the U.S. and would not necessarily replace other sweeteners. As a result, Pepsi, of Purchase, N.Y., said the new SoBe Life drink will be rolled out first in several Latin American markets, starting in Peru.

Coke teamed with Cargill Inc. to

Coke are working are already starting tabletop versions of their sweeteners, moves meant to build consumer awareness and interest. In May, Whole Earth Sweetener Co., a Merisant Co. unit, and Cargill submitted data to the FDA that they hope will clear the sweeteners as safe for use in foods and beverages in the U.S.

After a series of studies suggested some negative health effects from stevia-based products, such as potential mutations in the livers of rats and concerns about fertility in men, the FDA concluded in the early 1990s that there were not enough data available to demonstrate stevia’s safety as a food additive, although it is approved for use as a dietary supplement in the U.S. Stevia has been approved for use in foods in 12 countries, including Argentina, Brazil, China and Peru. Coke, Pepsi and the companies they are working with dispute the earlier studies and say their new product is purer than unrefined versions of stevia used in some of those tests.

Cargill introduced Truvia, its tabletop version, this month. It is available online and at a few New...
Brazilian fruits with high economic value

“Guaraná”
Paullinia cupana Kunth (Sapindaceae)

“Cajá”
Spondias mombin L. (Anarcadeaceae)

“Pitanga”
Eugenia uniflora L. (Myrtaceae)

“Açai”
Euterpe oleracea Mart (Arecaceae)

“Umbu”
Spondias tuberosa Arr. (Anarcadeaceae)

“Jaboticaba”
Myrciaria jaboticaba (Vell.) Berg, (Myrtaceae)
Feijoa sellowiana Berg., Myrtaceae

Brazilian Pharmaceutical Industry
Brazilian Pharmaceutical Industry
Brazilian Pharmaceutical Industry

CAPSULAS GELATINOSAS

DE

OLEO DE CAPIVARA

compostas com IODO e GLYCERO-PHOSPHATO

Incomparável remedio para o tratamento da

Tubercolese, Anemia, Neurasthenia, etc.

Usadas com constância determinam aumento considerável de

PESO e DESENVOLVIMENTO MUSCULAR

notáveis pela sua ação de reconstituir o sangue vitioso.

Não perturbam as funções do estômago ou intestinos

e são consideradas como excelente regularizador da saúde.

Silva Araujo & C.

RUA 1º. DE MARÇO Ns. 1 e 3

RIO DE JANEIRO

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Hydrochoerus hydrochaeris, Capiviidae
The Especifico Pessoa: An Antidote against *Bothrops atrox* snake venom

*Bothrops atrox*
The Especifico Pessoa: An Antidote against Bothrops atrox snake venom

Prof. Koji Nakanishi
Columbian University
The active compounds isolated from *Especifico pessoa*

- Injection of 2.5mg/kg venom to 9kg beagle dog leads to hypotension, respiratory and cardiac arrest.

- Injection of 1 mg/kg of A-I, 15 min before or after venom injection restores or reverses effect in 90 min.

Amazônia

- A floresta vira fazenda
- Existe um futuro sustentável?
- O novo papel dos índios

1º MAIO O canto das baleias jubarte
A caça aos tesouros na Eslovênia
The arrival of soy bean in Amazon

Fuente: Instituto de pesquisa ambiental da Amazônia

El total de queimadas en la región amazónica en el período de 1999-2005 (km²)
BRAZIL has a Great Potential in Research

Number of articles published in international journals

Masterdegree and PhD per year

The Brazilian scientific production represents 1.8% of the world production (17º position in 2005)

Fonte: CNPq / MCT

10 thousand PhD’s annually

Fonte: Capes / MEC
Ph.D researchers

University x Company

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### Faltam pesquisadores nas empresas brasileiras

A maior parte dos cientistas dos países ricos trabalha em empresas privadas. No Brasil, a situação se inverte. Eles se concentram nas universidades, a maioria das quais é mantida com dinheiro público. Um estudo feito pela Universidade de Brasília concluiu que esse fato atrapalha a inovação e traz prejuízos à competitividade das empresas brasileiras.

#### ONDE TRABALHAM OS CIENTISTAS

<table>
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<th>Empresas</th>
<th>Universidades</th>
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<td>80%</td>
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<td>32%</td>
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<td>BRASIL</td>
<td>27%</td>
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<td>ARGENTINA</td>
<td>12%</td>
<td>45%</td>
<td>43%</td>
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Fonte: Universidade de Brasília
Aché Laboratories

• The biggest pharmaceutical company in Latin America
• Benefices 2005: U$ 800 millions (Ethics synthetic lines and OTC)
• production : 150 millions units/year
• Number of workers : 5,000
• Sales force : 1,200 representatives visiting 130,000 physicians / month
Modern drug production
Aché’s Laboratory Capacity

Products:

1. Solids (72 millions units/year)
2. Liquids (60 millions units/year)
3. Semisolids (12 millions units/year)
Aché’s R&D Pipeline

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<th>Projects</th>
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<th>Pharmaceutical form development</th>
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Aché partners

University of Geneva, Switzerland
University of Barcelona, Spain
Acheflan®

The first drug developed in Brazil
Cordia Verbenacea D.C., Boraginaceae

C. Verbenaceae could be found in the Atlantic rain forest
GC/MS analysis of *C. verbenaceae* essential oil

Fraction 1 (monoterpenes)  
1 2 3 4 5  
6 7

Fraction 2 (sesquiterpenes)  
8 9 10  
11 12 13 14

- **β-cubebene**
- **δ-cadinene**
- **α-copaene**
- **α-humulene**
- **δ-elemene**
- **bisabolol**
- **Zingiberene**
- **trans-cariophylene**
Effect of systemic treatment with α-humulene and trans-caryophyllene from *Cordia verbenacea* on bradykinin (BK)-induced paw oedema in mice

Effect of systemic treatment with \( \alpha \)-humulene and \textit{trans}-caryophyllene from \textit{Cordia verbenacea} on platelet-activating factor (PAF)-induced paw oedema in mice

Acheflan’s industrial production

Selection of plants → Cultivation → Industrial collection

- Formulation
- Quality control, ...

Extraction of the essential oil
Brazilian Market of Topical Anti-inflammatory Drugs 2003-2007

Year | Acheflan® | Cataflam® | Biofenac® | Scaflam® | Feldene® | Profenid® | Generics®
--- | --- | --- | --- | --- | --- | --- | ---
2003 | 0,0% | 15,7% | 26,4% | 6,3% | 7,4% | 3,9% | 3,1%
2004 | 0,0% | 14,9% | 27,5% | 6,8% | 6,6% | 4,0% | 4,2%
2005 | 7,1% | 18,5% | 21,0% | 7,1% | 4,5% | 4,3% | 8,0%
2006 | 27,9% | 15,7% | 18,6% | 6,6% | 4,0% | 3,6% | 6,1%
2007 | 40,7% | 12,9% | 14,3% | 6,6% | 2,7% | 3,7% | 5,7%
Acheflan® sales in 2009

Acheflan® has 49% of the medical prescriptions

sales 80.000 unit monthly
Cordia verbenacea PROJECT

- New indications and formulations:
  - Oral
  - Path
  - Osteoarthritis
  - Dermatological affection
The "Passion" in "passion flower" does not refer to sex and love however, but to the passion of Jesus Christ. In the 15th and 16th centuries, Spanish Christian missionaries adopted the unique physical structures of this plant, particularly the numbers of its various flower parts, as symbols of the last days of Jesus Christ and especially the Crucifixion.

During the first World War preparations with Passiflora was used in soldiers to treat the shellshock-combat stress reaction.

Strategy for development of a new *Passiflora incarnata* L. extract

- Classical extraction method
  - Indolic alcaloids

*Passiflora incarnata* L.

C-glicosilados flavonoids
Strategy for development of a new *Passiflora incarnata* L. extract

- **Extraction method***
- **Purification Method***

*methodology has been patented by Aché

7% of total flavonoids

Pharmacological assays

21 mg of flavonoids/caps

C-glicosylated flavonoids
Standarization of the ACH6 extract

Uv of flavonoids

ACH06 extract

LC/UV/DAD analysis of the extract of *Passiflora incarnata*
Phytochemical study of the ACH06 extract

Isovitexin
Chemical Formula: C_{21}H_{20}O_{10}
Molecular Weight: 432.38

Extrato a 7% de flav. totais

Semiprep-HPLC

RMN 1D e 2D
RMN \textsuperscript{1}H
RMN \textsuperscript{13}C
RMN 500 MHz

Isolamento
Compounds identified from the ACH06 extract

- Vitexin
- Isovitexin
- Isoschafitoside
- Schafitoside
- Isovิตexin-2”-O-β-sophorose
- Isorientin-2”-O-β-sophorose
- Saponarine
- Vicenina 2’
Sintocalmy®
Thank you for your attention

Emerson.queiroz@ache.com.br

Prof. Bejamin Gilbert
Prof. Walter Mors
Prof. Otto Gottlieb