CHEMICAL PROSPECTING FROM INDONESIAN RAINFOREST PLANTS

Sjamsul Arifin Achmad, Euis Holisotan Hakim, Lia Dewi Juliawaty, Lukman Makmur, Didin Mujahidin and Yana Maolana Syah

Research Group on Natural Product Chemistry
Department of Chemistry
Institut Teknologi Bandung
Indonesia
DRUGS DISCOVERY PROGRAM

ACQUIRE BIODIVERSITY

FOR

BROADENING OF AVAILABLE MOLECULAR STRUCTURES (CHEMODIVERSITY)

FOR BIO- & AGRO-INDUSTRIES
SOME CONTEMPORARY ISSUES ON GLOBAL DEVELOPMENTS

ENVIRONMENT
BIODIVERSITY; BIOETHICS
FOODS & HEALTH
ENERGY; MATERIALS
INFORMATION TECHNOLOGIES
**NATURAL PRODUCTS IN DEVELOPMENT OF MEDICINES**

- Over 120 drugs of known structures still extracted and produced commercially from only 90 species of higher plants, and used globally as a single agent drugs.

- During 1959-1980, in United States, 25% of all prescriptions dispensed from pharmacies contained active principles extracted from higher plants. In 1980, consumers in the United States paid more than US$ 8 billion for prescription containing active principles from higher plants.

- During 1989-1995, over 60% of approved anticancer and antiinfective agents, are of natural origin.

- Over 60% of world’s population use plants as a primary health care.

- About $ 5.00 billion are used on phytotherapeutical in U.S. in 2005.
GLOBAL HEALTH PROBLEMS

- No globally available treatments for new deadly and untreatable diseases (AIDS, tuberculosis, malaria, avian flu)

- Increasing drug resistance

- Exploding population
THE POTENTIAL OF NATURAL PRODUCTS IN HEALTH CARE

Natural product sciences must contribute in:

• Drug discovery for critical diseases

• Enhance natural product structure diversification

* Phytotherapeutical standardization

Sustainable drug discovery approaches are urgently needed for future health care
WHAT NEXT ???

THERE IS NO DOUBT THAT PLANTS HAVE PROVIDED, AND CAN CONTINUE TO PROVIDE HUMANS WITH USEFUL DRUGS.

NOBODY COULD NEGLECT TO INVESTIGATE FURTHER THE ABUNDANT FLORA OF THE WORLD FOR THE PRESENCE OF NEW DRUGS THAT WILL BENEFIT THE WORLD.
BIORESOURCES

TERRESTRIAL OR MARINE ANIMALS, PLANTS AND MICROORGANISMS ARE CHEMICAL SYSTEMS, ULTIMATE CHEMICAL SOURCE, AND CHEMICAL SAFETY IN THE 21TH CENTURY
GENETIC RESOURCES OF SOUTHEAST ASIA
A SPECIAL HERITAGE

1. EVERGREEN TROPICAL RAINFOREST
2. OLDEST & MOST DIVERSE TERRESTRIAL ECOSYSTEM
3. ABUNDANCE & UNPARALLELED GENETIC VARIATIONS & HIGHLY SPECIALIZED VEGETATION
4. RICH SOURCE OF NATURAL PRODUCT CHEMICALS
SYSTEMATIC STUDY ON CHEMICAL DIVERSITY OF PLANT SPECIES FROM INDONESIAN TROPICAL FORESTS
PHYLOGENETIC RELATIONSHIP BETWEEN PLANTS FAMILIES
EVOLUTIONARY RELATIONSHIP BETWEEN SUB-CLASSES OF DICOTYLEDONE

WHY LAURACEAE ???

• Large family consists of 3000 species from the most primitive sub-class Magnoliidae of the flowering plants

• Tropical plants, 600 species are found and widely distributed in Indonesia

• Has been used as traditional medicines, edible fruits, spices, perfume oils and for its timber

• Exhibited useful biological activities

• Contains interesting class of natural product compounds

• Largely unexplored
DISTRIBUTION OF LAURACEAE IN INDONESIA
EVOLUTIONARY AFFINITIES AMONG SUBTRIBES OF LAURACEAE (KOSTERMANS, 1957)

PERSEINEAE
BEILSCHMIEDINEAE

CINNAMOMINEAE

LITSEINEAE
LAURINEAE

ANABINEAE

CRYPTOCARYINEAE
EUSIDEROXYLEINEAE
CHEMICAL RELATIONSHIP BETWEEN VARIOUS SUBTRIBES OF LAURACEAE (GOTTLIEB, 1972)

PERSEINEAE
BEILSCHMIEDINEAE
Alkaloid precursor

CINNAMOMINEAE
Alkaloids A
Arylpropanoids

LITSEINEAE
LAURINEAE
Alkaloids
“Advanced” Flavonoids
Sesquiterpenes

CRYPTOCARYINEAE
Alkaloids A,B,C
Arylpropanoids

ANABINEAE
“Primitive” Arylpropanoid
2-Pyrones
Flavonoids
Benzophenone
**PHARMACOLOGICAL ACTIVITY OF SOME OF THE LAURACEAE**

<table>
<thead>
<tr>
<th>Species</th>
<th>Pharmacological activities</th>
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</thead>
<tbody>
<tr>
<td><em>Actinodaphne nitida</em> Teschn.</td>
<td>Cardiovascular; Antispasmodic</td>
</tr>
<tr>
<td><em>Beilschmiedia elliptica</em> C. White</td>
<td>Cardiovascular; Analgesic; Antipyretic</td>
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<tr>
<td><em>B. podagrica</em> Kosterm.</td>
<td>Central nervous system; cardiovascular;</td>
</tr>
<tr>
<td><em>Cassytha filiformis</em> L.</td>
<td>Diuretic</td>
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<tr>
<td><em>Cinnamomum baileyanum</em> (F.Muell ex Bailey) Francis</td>
<td>Antitumor</td>
</tr>
<tr>
<td><em>Cryptocarya bowiei</em> Druce</td>
<td>Antitumor</td>
</tr>
<tr>
<td><em>C. fluminensis</em> Kosterm.</td>
<td>Antitumor;</td>
</tr>
<tr>
<td><em>C. laevigata</em> Bl.</td>
<td>Hypotensive; Anticonvulsant; Analgesic</td>
</tr>
<tr>
<td><em>C. laevigata</em> var. bowiei</td>
<td>Antitumor</td>
</tr>
<tr>
<td><em>C. microneura</em> Meissner</td>
<td>Antitumor</td>
</tr>
<tr>
<td><em>C. multinervis</em> Teschn.</td>
<td>Antitumor</td>
</tr>
<tr>
<td><em>C. multipaniculata</em> Teschn.</td>
<td>Antitumor</td>
</tr>
<tr>
<td><em>C. pleurosperma</em> C. White</td>
<td>Antitumor; Vesicant; Hypotensive;</td>
</tr>
<tr>
<td><em>Litsea glutinosa</em> (Lour)C.E.Rob</td>
<td>Antitumor;</td>
</tr>
<tr>
<td><em>Litsea sp. aff. glutinosa</em> (Lour.)</td>
<td>Antiviral; Inhibitor protein synthesis</td>
</tr>
<tr>
<td><em>Litsea timoriana</em> Span.</td>
<td>Hypotensive; Analgesic; Antipiretic</td>
</tr>
<tr>
<td><em>Phoebe forbesii</em> Gamble</td>
<td>Antitumor</td>
</tr>
<tr>
<td></td>
<td>Antiinflamation; Diuretic</td>
</tr>
<tr>
<td></td>
<td>Hypotensif; Antimicrobial; Diuretic</td>
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<tr>
<td></td>
<td>Antitumor</td>
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<tr>
<td></td>
<td>Antiinflammatory, Diuretic</td>
</tr>
<tr>
<td></td>
<td>Hypotensive, Antimicrobial, Diuretic</td>
</tr>
</tbody>
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CHARACTERISTIC OF TARGETED FLORA

- LONG ISOLATION FOR UNIQUENESS OF FLORA
- HIGH ENDEMICITY
- WIDE VARIETY OF BIOTOPES
- DIVERSIFIED - FROM ANCESTRAL TO MODERN TAXA
- DISTRIBUTION OF SPECIES
CURRENTLY INVESTIGATED SPECIES OF INDONESIAN LAURACEOUS PLANTS

- Actinodaphne glomerata
- Cryptocarya strictifolia
- C. densiflora
- C. massoia
- C. ferrea
- C. idenburgensis
- C. kamahar
- C. laevigara
- C. nutans
- Litsea amara
- L. cassiaefolia
- L. cubeba
- L. diversifolia
- L. elliptica
- L. excelsa
- L. firma
- L. glurinosa
- L. grandis
- L. monoperala
- L. tomenrosa
- Neolitsea cassiaefolia
- Persea rimosa
INDONESIOL A NEW SESQUITERPENE FROM *LITSEA AMARA* BL. (LAURACEAE)

A NEW MAJOR SESQUITERPENE FROM
*LITSEA EXCELSA* NEES (LAURACEAE)

NEW SESQUITERPENES FROM *LITSEA CASSIAEFOLIA* BL. (LAURACEAE)

Litseacassifolide


Isocurcumol
DEGREE OF BIOGENETIC COMPLEXITY OF NEW SESQUITERPENES DERIVED FROM LAURACEAE

Indonesiol (Secoiswarane)
8-Hidroxycusunol (Eremofilane)
Isocurcumol (Guaian)
Litseacassifolide (Germacrane)
Neoserisealactonic acid (Elemene)
WHY MORACEAE ???

• MORACEAE CONSISTS OF 50 GENERA AND 1500 SPECIES IN THE FORM OF TREE OR SHRUBS BUT RARELY HERBS

• MOSTLY FOUND IN TROPICAL AND SUB TROPICAL ZONES

• MORE THAN 80 SPECIES MAY BE FOUND IN INDONESIA. HOWEVER SCIENTIFICALLY UNEXPLORED

• ECONOMICALLY IMPORTANT AS EDIBLE FRUITS, MEDICINAL PLANTS, FOOD FOR SILKWORMS, FLAVOURINGS, TIMBERS

• PRODUCE INTERESTING CHEMICALS: SUCH AS FLAVONOID, XANTHONE, STILBEN, ARYLBENZOFURAN, DIEL-ALDER TYPE ADDUCT, ALKALOID AND CARDENOLIDE

• EXHIBITED USEFUL BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES: ANTI-HYPERTENSIVE, ANTITUMOR, ANTIDIABETIC, ANTI MICROBIAL, JUVENOMIMETIC
CURRENTLY INVESTIGATED SPECIES OF INDONESIAN MORACEOUS PLANTS

- Artocarpus altillis (Park) Fobs.
- Artocarpus bracteata
- Artocarpus champeden
- Artocarpus dadah Miq.
- Artocarpus dasyphyllus
- Artocarpus gomezianus Wall.
- Artocarpus kemando
- Artocarpus lanceifolius
- Artocarpus maingayii
- Artocarpus nitidus Trec.
- Artocarpus reticulatus
- Artocarpus rotundas
- Artocarpus scortechinii
- Artocarpus teysmanii
- Artocarpus sp.
- Morus macroura Miq.
Degree of biosynthetic complexity and cytotoxicity against P-388 cell-line of the flavonoids derived from *Artocarpus*
PHYLOGENETIC RELATIONSHIP BETWEEN SOME SPECIES OF ARTOCARPUS

A. altissimus
A. dadah
A. lackoocha
A. elasticus
A. altilis
A. lanceifolius
A. nitidus
A. rigidus
A. heterophyllus
A. integer
Morus
Ficus
A. chaplasha
A. lackoocha
A. altissimus
A. dadah
WHY DIPTEROCARPACEAE ???

• A LARGE FAMILY OF TROPICAL PLANTS, COMPRISSES 16 GENERA AND 600 SPECIES. THE LARGEST GENERA, SHOREA (150 SPECIES) KNOWN LOCALLY AS MERANTI.

• ESPECIALLY ABUNDANT IN THE RAINFOREST OF INDONESIA, HOWEVER A GREAT MAJORITY HAVE NOT BEEN INVESTIGATED

• HIGHLY VALUED FOR THEIR TIMBER WHICH ARE USED IN BUILDING CONSTRUCTIONS, MEDICINAL APPLICATION AND SPICES

• CONTAINS VARIETY OF ATTRACTIVE PHENOLIC COMPOUNDS, INCLUDING OLIGOSTILBENOID, FLAVONOID, AND PHENYLPROPANOIDS

* MANY OF THE STILBENOID SHOWED USEFUL BIOLOGICAL ACTIVITIES: ANTI-HIV, ANTIBACTERIAL, ANTIFUNGAL, ANTIINFLAMMATION, CYTOTOXIC, HEPATOPROTECTIVE, INHIBITOR 5α-REDUCTASE AND ACETYLCHOLINE ESTERASE.
CURRENTLY INVESTIGATED SPECIES OF INDONESIAN DIPTEROCARPACEAE

- *Anisoptera marginata* Korth.
- *Dipterocarpus grandifolius* Blco.
- *Dipterocarpus intricatus*
- *Dryobalanops oblongifolia*
- *Hopea dryobalanoides*
- *Shorea balangeran* Burck.
- *Shorea multiflora* Burck.
- *Shorea guiso* Blume
- *Shorea leprosula* Miq.
- *Shorea pinanga* Scheff.
- *Shorea selanica* Blume
- *Shorea seminis V. SI.*
- *Shorea stenoptera*
- *Vatica pauciflora* Blume
- *Vatica umbonata* Korth.
DIPTOINDONESIN-A AND RELATED STILBENOIDS FROM SHOREA SEMINIS

cis- AND trans-DIPTOINDONESINS - B FROM DRYOBALANOPS OBLONGIFOLIA (DIPTEROCARPACEAE)

\[ \text{cis-Diptoindonesin - B} \quad \text{trans-Diptoindonesin - B} \]

DIPTOINDONESINS C - E FROM VATICA PAUCIFLORA (DIPTEROCARPACEA)

R=H : Diptoindonesin - C
R=Gluc : Diptoindonesin - D

Diptoindonesin - E
SOME FURTHER STILBENOIDS FROM VATICINA PAUCIFLORA (DIPTEROCARPACEA)

e-Viniferin

Ampelopsin F

Stenophylol B

Copallyferol A

Vaticanol G
DIPTOINDONESIN - F AND NEW STILBENOID (+) – STENOFILLOLL FROM DIPTEROCARPUS INTRICATUS DYER. (DIPTEROCARPACEAE)

(+)-DIPTOINDONESIN - F

(+)-STENOFILLOLL - C
DIPTOINDONESIN - G AND RELATED STILBENOIDS FROM HOPEA DRYOBALANOIDESES MIQ

Literature:
SOME FURTHER STILBENOIDS FROM HOPEA DRYOBALANOIDES MIQ

HEIMIOL A

α-VINIFERIN

VATIKANOL B

HOPEAPHENOL
DIPTOINDONESIN – H FROM SHOREA PINANGA SCHEFF (DIPTEROCARPACEAE)

Diptoindonesin - H

Ampelopsin - E

Literature:
SOME FURTHER STILBENOIDS FROM SHOREA PINANGA (DIPTEROCARPACEAE)

Laevifonol

Ampelopsin A

a - Viniferin

Hopeaphenol

Literature:
CYTOTOXICITY OF STILBENOIDS AGAINST HL 60 CELL LINES

- e-Viniferin
  IC50 0.8 ug/mL

- Laevifonol
  IC50 0.9 ug/mL

- Balanocarpol
  IC50 0.6 ug/mL

- a-Viniferin
  IC50 2.1 ug/mL

- Hopeaphenol
  IC50 0.4 ug/mL
ANTIOXIDANT ACTIVITY OF STILBENOIDS

Resveratrol
IC50 85.6 ug/mL

Oxyresveratrol
IC50 25.8 ug/mL

Oxyresveratrol gluc.
IC50 58.9 ug/mL

e-Viniferin
IC50=121.4 ug/mL

a-Viniferin
IC50 284.5 ug/mL

cis-Diptoindonesin B
IC50 76.6 ug/mL

trans-Diptoindonesin B
IC50 91.2 ug/mL
THE MAIN GATE OF INSTITUT TEKNOLOGI BANDUNG (ITB)  
JALAN GANECA 10, BANDUNG, INDONESIA
RESEARCH GROUP OF NATURAL PRODUCTS CHEMISTRY
Department of Chemistry, Institut Teknologi Bandung
RESEARCH GROUP OF NATURAL PRODUCTS CHEMISTRY
Department of Chemistry, Institut Teknologi Bandung

THANK YOU
RADICAL TRANSFORMATION OF OLIGOSTILBENOIDS
ARRANGEMENT OF STILBENOID DIMERS AND TRIMERS BY BIOGENETIC COMPLEXITY OF CARBON SKELETON FROM DIPTEROCARPACEAE
ARRANGEMENT OF STILBENOIDS BY BIOGENETIC COMPLEXITY OF CARBON SKELETON FROM DIPTEROCARPACEAE