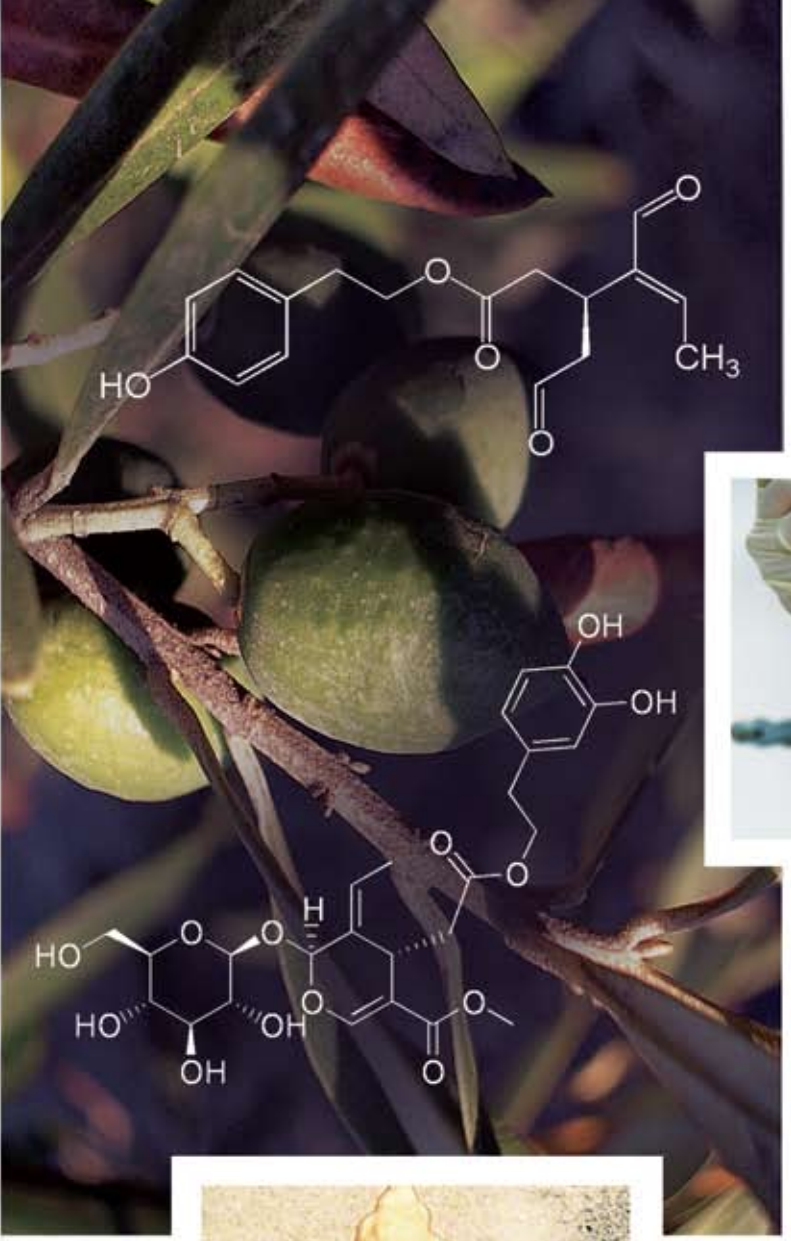
National and Kapodistrian University of Athens



Natural Product and Medicinal Chemistry Research Group

Departments of Pharmacognosy and Medicinal Chemistry - Faculty of Pharmacy

Our Mission

Since 1994, the group has focused its activities on the discovery of small molecules –natural products and synthetic derivatives – as lead compounds for pharmaceutical, neutraceutical, cosmeceutical and agrochemical applications.

The Team

The Natural Products and Medicinal Chemistry Research Group is based on the collaboration of the Department of Pharmacognosy and the Department of Medicinal Chemistry of Faculty of Pharmacy, National and Kapodistrian University of Athens (NKUA). The research team consists of 45 highly qualified experts in natural product and medicinal chemistry research – 11 academic staff members, 12 postdoctoral researchers, 10 PhD students, 9 postgraduate students and 3 technicians.

Natural Products and Medicinal Chemistry Research Group

Faculty of Pharmacy - University of Athens

Research activities

Phytochemistry

Discovery of bioactive compounds from plants, fungi and marine organisms from Mediterranean and global biodiversity.
Development and application of protocols for the production of extracts / enriched extracts, using modern techniques.
Isolation and structural elucidation of bioactive compounds using state of the art Nuclear Magnetic Resonance and Mass Spectrometry techniques .

Synthesis

Total synthesis of natural products.
Semi-synthesis of natural product derivatives.
Design and synthesis of potentially bioactive molecules.
Structure – activity relationship studies.

Analysis

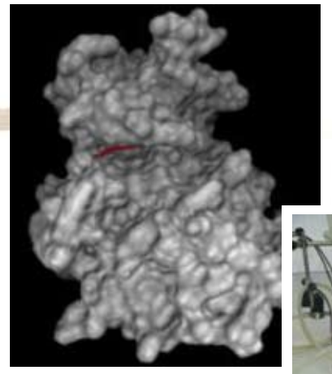
Profiling and fingerprinting of natural extracts (plants, food, nutraceuticals).
Pharmacokinetic studies of natural products.
Development of UPLC and LCMS methods for quantification of natural products in biological fluids.

Metabonomics

LC and NMR based metabonomics in human biofluids and plant extracts

In silico studies and biological evaluation

In silico ADME predictions.
Molecular dynamics simulation and docking studies (protein-ligand interactions).
Establishment of receptor – ligand interactions .
Evaluation of antioxidant and antiaging properties of natural products by *in vitro* and bioautographic assays.



Applications

- "Green" technology applications for extraction of bioactive compounds (e.g. CO_2 extraction of mountain tea , black truffles, olive oil)
- Method development for isolation of bioactive compounds (e.g. oleocanthal and oleuropein from olive oil)
- Design and synthesis of novel CDK, GSK-3 inhibitors (e.g. indirubin derivatives)
- Targeted isolation and/or synthesis of Selective Estrogen Receptors Modulators (e.g. isolation of isoflavones from Leguminosae plants)
- HPLC and UPLC method development for identification of biomarkers in plant extracts (e.g. in wines, mountain tea)
- NMR based metabonomics for the discovery of biomarkers in human fluids (e.g. identification of novel biomarkers)
- Treatment of agricultural waste aiming to the large scale production of high added value natural products (e.g. from olive, grapes, tomato, sesame and rice)
- Development of functional foods and beverages enriched with bioactive compounds / extracts (e.g. yogurt containing oleuropein)
- Lab scale to pilot scale production of aromas from cultivated plants (e.g. roses, chamomile and pistacia)
- Fermentation and extraction of bioactive compounds from microorganisms (e.g. production of naphthoquinones from terrestrial fungi, isolation of indole derivatives from human pathogen fungi)

Infrastructure

The laboratories are fully equipped with state of the art instruments required for the implementation of our research activities. In detail:

Laboratory scale

Extraction

Maceration unit, Accelerated Solvent extraction unit (ASE), Supercritical Fluid Extraction unit (SFE), Microwave Assisted Extraction unit (MAE)

Isolation

One High Speed Counter Current Chromatography unit (HSCCC) with 500 mL and 1000 mL columns connected to auto collector, two preparative and semi preparative High Performance Liquid Chromatography systems (HPLC) coupled with various detectors, two preparative Medium Pressure Liquid Chromatography systems (MPLC) coupled with auto-collector.

Synthesis and *in silico* studies

Buchi Syncore apparatus for combinatorial synthesis, four Silicon Graphics workstations, Linux cluster and software.

Analysis

Three analytical HPLC systems equipped with autosamplers and coupled with Diode Array (DAD-UV), Evaporative Light Scattering (ELSD) and Refractive Index (RI) detectors, one LC-MS system equipped with ESI and APCI ionization sources, one UPLC system coupled to DAD detector and interfaced to a High-Resolution MS (Orbitrap hybrid linear ion trap) equipped with ESI, APCI and APPI ionization sources, two GC-MS systems with EI and CI ionization sources, one head-space analysis GC-MS and one GC-FID apparatus, one HPTLC Camag platform including an applicator and a scanner for densiometric applications.

Structural elucidation

Three NMR spectrometers of 200, 400 and 600 MHz, the latter being equipped with both 5 mm and 1mm probes and a 60- position autosampler, additional equipment of mass spectrometers, FT-IR, UV/vis, polarimeter, melting point apparatus.

Formulation

One spray dryer equipped with inert loop, two lyophilization units, 2D barcoding system for encoding and storage.

Fermantation & Bioevaluation

Two incubators, one bioreactor, one autoclave, one plate reader

Pilot scale

Distillation / extraction unit of 1000 L, distillation unit of 200 L, essential oil distillator of 100 L, two extraction vessels of 500 and 600 L respectively, adsorption resin columns (XAD4 and XAD7) with a capacity of 150 L (x4) and 450 L (x2), vacuum dessicator of 100 L, three rotary evaporators of 20 L each, one lyophilization unit, a 63 L reactor for medicinal chemistry preparations.

Biological and Chemical Recources

Biomaterial

Collection of more than 600 plants collected throughout the Mediterranean biodiversity hotspot. More than 1/5 of them are endemic.

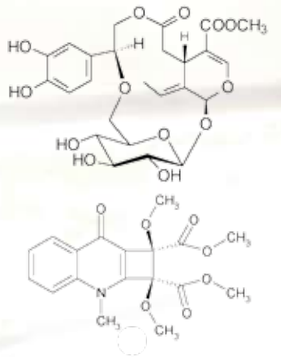
Collection of marine organisms and fungi, including 100 basidiomycetes from Greek forests and 500 cultivated strains.

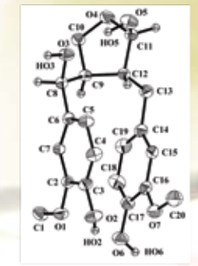
Access to biomaterial of the Mediterranean basin, Asia (Mongolia), South and Central America (Brazil, French Guiana, Panama), Africa (Nigeria, Cameroon, Morocco) and Oceania (New Caledonia)

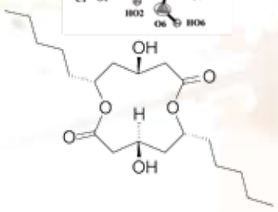
Chemical library

More than 5000 extracts of plants, fungi and marine organisms

Chemical libraries with more than 2000 commercially unavailable compounds consisting of natural products with unique chemical structures and novel scaffolds, and synthetic / semi-synthetic compounds







Publications

More than 250 peer reviewed publications in international journals like Nature Medicine, Oncogene , Antimicrobial Agents & Chemotherapy, Chemistry &.Biology J. Medicinal Chemistry, J. Natural Products, J. Agriculture & Food Chemistry

More than 2500 citations
23 PhD thesis and 32 MSc thesis graduated students since 2000

Selected Publications

N. Sato et al. Maintenance of pluripotency in human and mouse embryonic stem cells through activation of Wnt signalling by a pharmacological GSK-3-specific inhibitor. Nature Medicine 2004, 10, 55-63.

N. Fokialakis et al. A New Class of Phytoestrogens: Evaluation of the Estrogenic Activity of deoxybenzoins. Chem.Biol. 2004, 11, 397-406.

P. Polychronopoulos, et al. Structural basis for the synthesis of indirubins as potent and selective inhibitors of glycogensynthase kinase -3 and cyclin-dependent kinases. J. Med. Chem 2004, 47, 935-946.

F. Bazoti, et al. Development of a Liquid Chromatography Electrospray Tandem Mass Spectrometry (LC-ESI MS/MS) method for the quantification of bioactive substances present in olive oil mill waste waters. Anal. Chem. Acta, 2006, 573, 258-266.

S. Paraschos, et al. *In vitro* and *in vivo* activity of Chios mastic gum extracts and constituents against *Helicobacter pylori*. Antimrob. Agents Chemother, 2007, 51, 551-559.

K.. Vougogiannopoulou, et al. Soluble 3′,6-substituted indirubins with enhanced selectivity towards glycogen synthase kinase-3. J. Med. Chem. 2008, 51, 6421-31.

S. Djiogue, et al. Isoflavonoids from *Erythrina poeppigiana* O. F. Cook: evaluation of their binding affinity for the Estrogen Receptor. J. Nat. Prod. 2009, 72, 1603-1607.

I. Andreadou, et al. Metabonomic identification of novel biomarkers in doxorubicin cardiotoxicity and protective effect of the natural antioxidant oleuropein. NMR Biomed. 2009, 22, 585-592.

K. Vougogiannopoulou, et al. The raputindoles: novel cyclopentyl bisindole alkaloids from *Raputia simulans*. Org. Lett. 2010, 12, 1908-1911

A. Urbain, et al. Hydrostatic countercurrent chromatography and ultra high pressure LC: Two fast complementary separation methods for the preparative isolation and the analysis of the fragrant massoia lactones. J. Sep. Sci. 2010, 33, 1198-1203

Grants

European Research grants

FP7-PEOPLE-2010-IRSES. CHEM BIOFIGHT project: Exploring the Chemical Biodiversity with Innovative Approaches to Fight Chagas Disease and Leishmaniasis (2011-2015)

FP7 Research, Technological Development & Demonstration Activities. AGROCOS project KBBE-2009 -3-1-04 "From Biodiversity to Chemodiversity: Novel Plant Produced Compounds with Agrochemical and Cosmetic interest" (2010-2014)

FP7-PEOPLE-IAPP-2008 230763 Marie Curie Actions. OLITEC project: «Bioactive natural compounds extracted and isolated from olive tree using modern technologies: Probing into their therapeutic potential» (2009-2013)

FP7-REGPOT-2007-1 CSA 206570. NATFORCE project: «Reinforcing Scientific and Technological Potential of the Natural Products Laboratory – University of Athens» (2008-2011)

LIFE 03 ENV/GR/000223 DIONYSOS: "Development of an economically viable process for the integrated management of winemaking industry waste; production of high added value natural products and organic fertilizer" (2003-2005). Top-5 best life environment project award

LIFE 00 ENV/GR/000671 MINOS: "Process development for an integrated olive oil mill waste management recovering natural antioxidants and producing organic fertilizer" (2001-2004). Best life environment project award

Selected National Grants

COOPERATIONS 2010 : Development of novel Angiogenesis-Modulating Pharmaceuticals by screening of natural compounds and synthetic analogues

COOPERATIONS 2010 : Development of natural products and derivatives thereof for the prevention and treatment of osteoporosis using transcriptomics, proteomics and matabonomics approach

EUREKA 2005: "Utilization of perisperm and other parts of the sesame plant for extraction and further isolation of bioactive compounds with high added value"

EPET 2004: "Design and development of new functional foods and food supplements, based on the Mediterranean diet and the biodiversity of the Greek flora."

International Collaborations

Industry

Pharmaceutical industry

Jannsen Pharmaceutica (Belgium)
Adir-Servier (France)
Pièrre-Fabre (France)
Intracellular Therapies (USA)
Lavipharm (Greece)
Pharmathen (Greece)
Galenica (Greece)
Elpen (Greece)

Agro-food industry

Frutarom (Switzerland)
Phytolab (Germany)
Finzelberg (Germany)
Hitex (France)
Mastic Gum Corporation (Greece)
Giotis (Greece)
Haitoglou (Greece)
Vivartia (Greece)
Elsap (Greece)
Cooperative wineries of Tyrnavos, Santorini, Robola (Greece)

Cosmetic industry

Korres Natural Products (Greece)
Apivita (Greece)

Others

BASF (Germany)
Bruker (Germany)
Biohellas (Greece)
Vioryl (Greece)
Terra Nova (Greece)

Academic / Research institutes

Université Paris V (France)
University of Basel (Switzerland)
Université de Geneva (Switzerland)
Oxford University (UK)
CNRS Station Biologique de Roscoff (France)
CNRS Gif-sur-Yvette (France)
University of Innsbruck (Austria)
University of Dresden (Germany)
USDA / University of Mississipi (USA)
Karolinska Institute (Sweden)
City of Hope (USA)
The Rockefeller University (USA)
Orsay Paris XI (France)
Institute Marie Curie Paris (France)
INRA Centre de Recherches de Clermont-Ferran (France)
University of Lublin (Poland)
Anadolu University (Turkey)
TMSTPC of Mongolia (Mongolia)
University of Cyprus (Cyprus)
Agricultural University of Athens (Greece)
NCSR Demokritos (Greece)
National Research Foundation (Greece)
Biomedical Research Foundation (Greece)
Benaki Phytopathological Institute (Greece)

Success stories

- Five indirubin analogues discovered by the team are in the market as pharmacological tools/biological reagents commercilized by several companies
- The discovery of 6BIO was announced in NATURE website hot news
- Several pure bioactive compounds from natural sources are available in large scale quantities

The discovery of 6BIO was announced in Nature website hot news

5 Indirubin analogues discovered by LNPC are in the market as pharmacological tools/ biological reagents commercialized by many companies

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