BIOTA-FAPESP PROGRAM

# DEVELOPMENT OF A PLATFORM FOR *IN VIVO* AND *IN VITRO* METABOLISM STUDIES WITH NATURAL PRODUCTS, A DEMAND FOR A SYSTEM OF PRE-CLINIC EXPERIMENTS

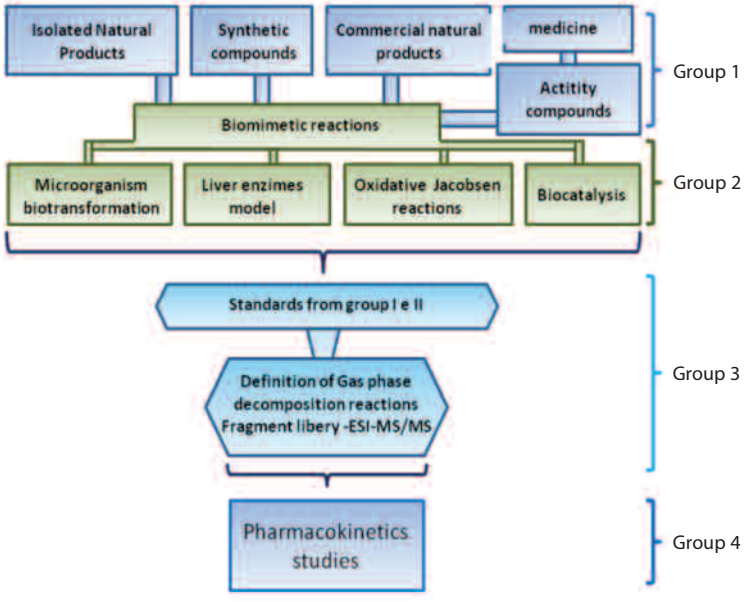
Norberto Peporine Lopes

Ribeirão Preto School of Pharmaceutical Sciences / University of São Paulo (USP)

Main researcher: Mônica Tallarico Pupo

FAPESP Grant 2009/51812-0 I Term: Jan 2010 to Dec 2013

Several actions for the development of bioactive natural products have been taken at national and state level, in majority ones that led to the identification of substances with therapeutic potential. A prerequisite for clinical and compound stability studies is the chemical characterization of active targets and also the elucidation of possible metabolites. In this context, the project aims the establishment of a working platform that envisions supporting pre-clinical studies, hereby generating four big working groups. Since the platform model still is somewhat uncommon the team size may oscillate during project execution, having involved in this first year seventeen members. The possibility of a variable group size occurs in function of the demand and opportunity of identifying a potentially active compound as well as having it in sufficient quantity for studies, which finally is the limiting factor for different works. Furthermore, the groups exhibit diverse characteristics concerning their publication potential and speed of obtaining results, which makes the global analysis a little different.

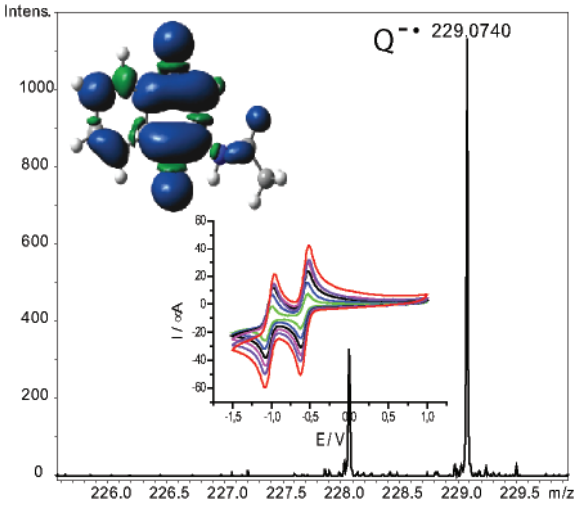



Group 1 (8 articles): Selection of bioactive natural and synthetic products

Group 2 (6 articles): *In vitro* metabolism studies of selected compounds in chemical and biological models. Obtainment of potential metabolites in larger scale

Group 3 (5 articles): Comprehension of decomposition reactions in gas phase by mass spectrometry (supported by theoretic calculations) from selected compounds and their derivatives, envisioning the creation of an ESI fragmentation spectra library

Group 4 (1 article): Application of the fragmentation models and obtained references for the development of analytical methods in in vitro and in vivo studies for absorption, kinetic disposition and also biotransformation of natural products

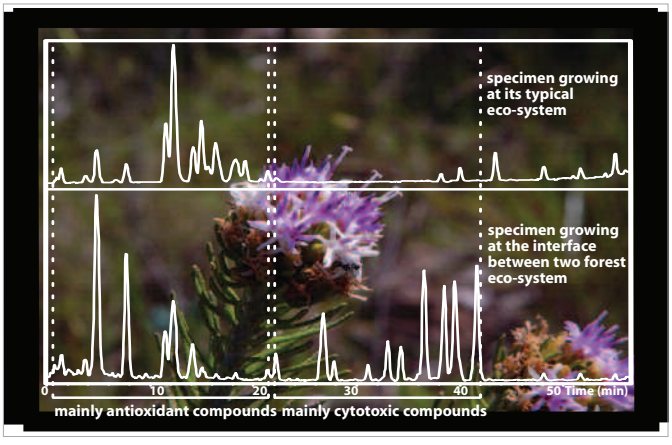



*Generation of naphthoquinone radical anions by electrospray ionization: comparison between solution and gas-phase chemistry*

## SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

The selected active natural products were submitted to biomimetic studies, in which the Jacobsen's catalyst was introduced instead of the more common metalloporphyrins, achieving for biomimetic reactions very high yields. In two cases, the yields of catabolized active compounds exceeded 90%, which is extremely significant. In two cases, the main products obtained by biomimetic reactions were the same as observed in the microsomal metabolism. This enabled the perspective of producing phase one metabolites for further pharmacokinetic analysis. The fragmentation studies in gas phase allowed the definition of three complete pathways from three classes of natural products. The first pharmacokinetic pilot study has clarified the elimination mechanism and half life time of the alkaloid piperine. Initial results has shown the viability of the proposal and has generated the expectation of better understanding the absorption, distribution and metabolization mechanism for selected natural products.

*Differential metabolic and biological profiles of* Lychnophora ericoides Mart. *(Asteraceae) from different localities in the Brazilian "campos rupestres"*




## MAIN PUBLICATIONS

Vessecchi R, Naal Z, Lopes JNC, Galembeck SE, Lopes NP. 2011. Generation of naphthoquinone radical anions by electrospray ionization: solution, gas-phase, and computational chemistry studies. *The Journal of Physical Chemistry*. A **115**: 5453-5460.

Crotti AEM, Gates PJ, Lopes JLC, Lopes NP. 2010. Electrospray MS-based characterization of b-carbolines mutagenic constituents of thermally processed meat. *Molecular Nutrition & Food Research* (Print) **54**: 433-439.

Guimarães DO, Borges WS, Vieira NJ, Oliveira LF, Silva CHTP, Lopes NP, Dias LG, Duran-Patron R, Collado IG, Pupo MT. 2010. Diketopiperazines produced by endophytic fungi found in association with two Asteraceae species. *Phytochemistry*. **71**: 423-1429.

Jabor VAP, Soares DM, Diniz A, Souza GEP, Lopes NP. 2010. LC-MS-MS identification and determination of the flavone-C-glucoside vicenin-2 in rat plasma samples following intraperitoneal administration of lychnophora extract. *Natural Product Communications.* **5**: 667-840.

Schaab EH, Crotti AEM, Iamamoto Y, Kato JM, Lotufo LV, Lopes NP. 2010. Biomimetic oxidation of piperine and piplartine catalyzed by iron(III) and Manganese(III) Porphyrins. *Biological & Pharmaceutical Bulletin.* **33**: 912-916.

Vessecchi R, Emery FS, Galembeck SE, Lopes NP. 2010. Fragmentation studies and electrospray ionization mass spectrometry of lapachol: protonated, deprotonated and cationized species. *Rapid Communications in Mass Spectrometry.* **24**:2101-2108.

Gobbo-Neto L, Guaratini T, Pessoa C, Moraes MO, Lotufo LVC, Vieira RF, Colepicolo P, Lopes NP. 2010. Differential metabolic and biological profiles of *Lychnophora ericoides* Mart. (Asteraceae) from different localities in the brazilian "campos rupestres". *Journal of the Brazilian Chemical Society.* **21**: 750-759.

Norberto Peporine Lopes

Faculdade de Ciências Farmacêuticas de Ribeirão Preto / Universidade de São Paulo (USP)

Departamento de Física e Química
Avenida do Café, s/n, Monte Alegre
CEP 14040-903 – Ribeirão Preto, SP – Brasil

+55-16-3602-4707
npelopes@fcfrp.usp.br