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17 au 19 juillet 2023

coorganisé avec l'OI METABIODIVEX, le GDR iNPChem, la GS HeaDS

Université Paris-Saclay, UFR Pharmacie

Bâtiment Henri MOISSAN, 17, avenue des Sciences, 91400 Orsay

Livre des résumés

Conférences : auditorium Hervé Daniel (bâtiment principal HM2)
Workshops : salle 2002, bâtiment HM1, 2e étage
Posters : RdC, bâtiment HM2

Wifi :	Réseau / network **"colloques"** ; mot de passe / password : **AmqaaMky**

https://aferp2023.sciencesconf.org/

Sommaire

Programme

Lundi 17 juillet

8:30-9:00 : Accueil

9:00-9:15 - Introduction

Pr Marc PALLARDY, doyen de l'UFR Pharmacie

Pr Delphine JOSEPH, directrice de la Graduate School HeaDS, codirectrice de BioCIS et de l'équipe Chimie des Substances Naturelles

9:15-10:45 - Conférences plénières

Modération : Dr. Bruno FIGADERE (CNRS, BioCIS)

9:15-9:45 *Conférence 1.* **Dr. Catherine ROULLIER** - *Halogenation in marine fungi: From metabolomics to biocatalysis*

9:45-10:15 *Conférence 2.* **Dr. Laurent EVANNO** - *Synthesis of* Piper *spp. alkaloids by photocatalytic assemblies of piperine*

10:15-10:45 *Conférence 3.* **Dr. Carine VERGNE-VAXELAIRE** - *Expanding the portfolio of enzymes for biocatalysis by extensive biodiversity screening*

10:45-11:15 - pause-café

11:15-12:30 - Communications courtes (15 min) n°1 à 5

Modération : Dr. Isabelle KERZAON (Lyon), Pr Olivier GROVEL (Nantes)

1	Manon MEUNIER	Matrix-free laser desorption ionization ion mobility mass spectrometry: A complementary approach to chemometrics in natural products research
2	Olivier BONNET	Identifications of minor and major metabolites from plants of *Strychnos* genus using molecular networking
3	Ramla SAHLI	Introducing natural deep eutectic solvents in Arizona solvent systems for sustainable use of centrifugal partition chromatography
4	Nangouban OUATTARA	Etude biologique et phytochimique de plantes médicinales antimicrobiennes de Côte d'Ivoire pour une valorisation thérapeutique contre *Toxoplasma gondii*
5	Blandine AKENDENGUE	Antifungal activity of *Petersanthius macrocarpus* (P.Beauv.) Liben trunk bark (Lecythidaceae)

12:30-14:00 pause déjeuner / session posters

14:00-14:30 - Conférences plénières

Modération : Pr Michel FREDERICH (Lièges)

14:00-14:30 *Conférence 4.* **Dr. Pierre Eric CAMPOS** - *Phytochemical study of ornamental plants cultivated in Centre-Val de Loire, France*

14:30-15:00 *Conférence 5.* **Dr. Jean-Luc CACAS** - *4-phenylbutyric acid, a « Swiss knife » molecule with high potential in agriculture*

15:00-15:30 *Conférence 6.* **Dr. Alexandre MACIUK** – Cannabis sativa *: variations autour d'un thème*

15:30-16:00 - pause-café

16:00-17:30 - Communications courtes (15 min) n°6 à 11

Modération : Pr Céline RIVIERE (UMR 1158, Lille), Dr. Laurent EVANNO (BioCIS, Paris-Saclay)

6	Grégoire AUDO (GILSON)[1]	Natural products purification by CPC-MS
7	Anne-Sophie PAGUET	Multiblock comparison of hop chemistry and its aromatic influence after brewing
8	Thomas CHARPENTIER	Natural Products Targeting the Unfolded Protein Response (UPR) as a New Biocontrol Strategy
9	Lúcia MAMEDE	Profiling plants with antimalarial blood stage activity using metabolomics: An added dimension to drug discovery
10	Elvis OTOGO N'NANG	Identification of tropical plant immune regulatory molecules inducing Mtb intracellular killing within infected macrophages to shorten TB therapy
11	Sufi DESRINI	Le séneçon en arbre et la renouée du Japon, des plantes invasives à potentiel anti-biofilm et antifongique

17:30-18:00 - Conférence plénière

Modération : Pr Céline RIVIERE (UMR 1158, Lille)

[1] sponsor du congrès

Conférence 7. **Dr. Séverine DERBRÉ** - *Finding needles in a haystack faster and more accurately? Proposed workflows combining chemometrics and dereplication based on both MS and ^{13}C NMR*

18:30-21:00 - ***Apéritif dinatoire*** *- Brass&Co, Orsay*

Mardi 18 juillet

9:00-11:00 - Conférences plénières

Modération : Pr Mehdi BENIDDIR (BioCIS, Paris-Saclay)

9:00-9:45 *Conférence 8.* **Pr Soizic PRADO** - *Chemistry of endophytic fungi: nature, ecological roles and applications*

9:45-10:30 *Conférence 9.* **Pr Andrew LAWRENCE** - *Biomimetic Natural Product Synthesis*

10:30-11:00 *Conférence 10.* **Dr. Kyo Bin KANG** - *Qualitative metabolomics for phenotyping of natural products biotransformation*

11:00-11:30 - pause-café

11:30-12:30 - Communications courtes (15 min) n°12 à 15

Modération : Dr. Sabrina BOUTEFNOUCHET (UMR CiTCoM, Paris-Cité), Dr. Pierre LE POGAM-ALLUARD (BioCIS, Paris-Saclay)

12	Emie Groppi	OSMAC approach applied to mycotoxins production by *Fusarium verticillioides*
13	Axel Leblond	Deep Chemical Exploration of Baldwin and Whitehead Biosynthetic Hypothesis for Manzamine Alkaloids Enabled by Data Science
14	Guillaume Hamion	L'acide bétulinique, un composé naturel prometteur contre les biofilms inter-règnes
15	Olivier Berry	Isolation of physiological regulators of *Prorocentrum lima* from an associated fungus *Aspergillus pseudoglaucus*

12:30-14:00 - pause déjeuner / ***session posters***

14:00-18:00 : ateliers

- **Workshop 1 : Déréplication RMN ^{13}C, MixONat**

Dr. Séverine DERBRE, Dr. Antoine BRUGUIERE

Pause-café

- **Workshop 2 : *Deep metabolome annotation (réseaux moléculaires LC-MS^2)***

Pr Mehdi BENIDDIR, Dr. Adriano RUTZ

Visites (sur inscription) :

- Conservatoire National des Plantes à Parfum, Médicinales et Aromatiques (**CNPMAI**, Milly-la-Forêt ; *en bus, retour sur Paris*)
- Musée François Tillequin de Matière médicale (UFR Pharmacie Paris-Cité)

19:30-22:00 - dîner de gala (Paris)

Mercredi 19 juillet

9:00-11 :00 - Conférences plénières

Modération : Pr Pascal RICHOMME (SONAS, Angers)

9:00-9:45 *Conférence 11.* **Pr Nadine ZIEMERT** - *Genome Mining Pipelines and Tools to Guide the Discovery of New Natural Products*

9:45-10:30 *Conférence 12.* **Dr. Fabrice NESLANNY** - *Genotoxicity of natural products*

10:30-11:00 *Conférence 13.* **Dr. Pierre LE POGAM-ALLUARD** - *From Châtenay-Malabry to Orsay: An odyssey into 60 years of phytochemistry*

11:00-11:30 - pause-café

11:30-12:45 - Conférences plénières

Modération : Pr Erwan POUPON (BioCIS, Paris-Saclay)

11:30-12:15 *Conférence 14.* **Pr Gérald CULIOLI** - *Chemistry of natural products and metabolomics applied to archaeometry and cultural heritage chemistry*

12:15-12:45 *Conférence 15.* **Dr. Charlotte SIMMLER** - *Tracing sponge specialized exometabolites in seawater sheds new light on their chemical diversity*

12:45-14:00 - pause déjeuner / ***session posters***

14:00-15:45 - Conférences plénières

Modération : Dr. Fanny ROUSSI (ICSN-CNRS)

14:00-14:45 *Conférence 16.* **Dr. Jean-Jacques HELESBEUX** - *Anti-inflammatory ω-oxidized tocotrienols modulating the arachidonic acid metabolism*

14:45-15:45 *Conférence 17.* **Pr Anne OSBOURN** - *Harnessing plant metabolic diversity for food and health applications*

15:45-16:15 - Remise des prix et clôture

Dr. Marc *LITAUDON, co-directeur de l'ICSN-CNRS, directeur de l'OI METABIODIVEX*

Pr Pierre *CHAMPY, président de l'AFERP*

Conférenciers invités

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Conférences plénières : résumés

Conférence 1

HALOGENATION IN MARINE FUNGI : FROM METABOLOMICS TO BIOCATALYSIS

COCHEREAU Bastien[1], GEROMETTA Elise[1], PUEL Olivier[2], HOLLMANN Frank [3], TASDEMIR Deniz[4], MESLET-CLADIERE Laurence[5], ROULLIER Catherine[1].

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While halogenated compounds represent a significant proportion of molecular entities in clinical studies for therapeutics, previous studies in our lab have shown the potential of marine fungi in the production of natural halogenated compounds **[1, 2]**. By investigating both metabolomes and genomes of different strains collected in marine environments, our studies have detected not only several new molecules but also versatile enzymes (vanadium HaloPerOxidases, vHPO) able to catalyze the halogenation of various substrates. From these results, different experiments have been carried out to both describe and understand the mechanisms involved in halogenation in these organisms, but also to propose innovative strategies (by biocatalysis) to obtain halogenated molecules of interest for therapeutics **[3, 4]**. Our studies then intend to provide solutions based on Nature, more respectful of the environment, to fight against antibiotic resistance in particular (Figure 1). In this presentation, we will focus on the results obtained in terms of characterization of halogenated compounds, production of halogenation enzyme(s), their use in biocatalysis and preliminary bioassays on the ESKAPE panel.

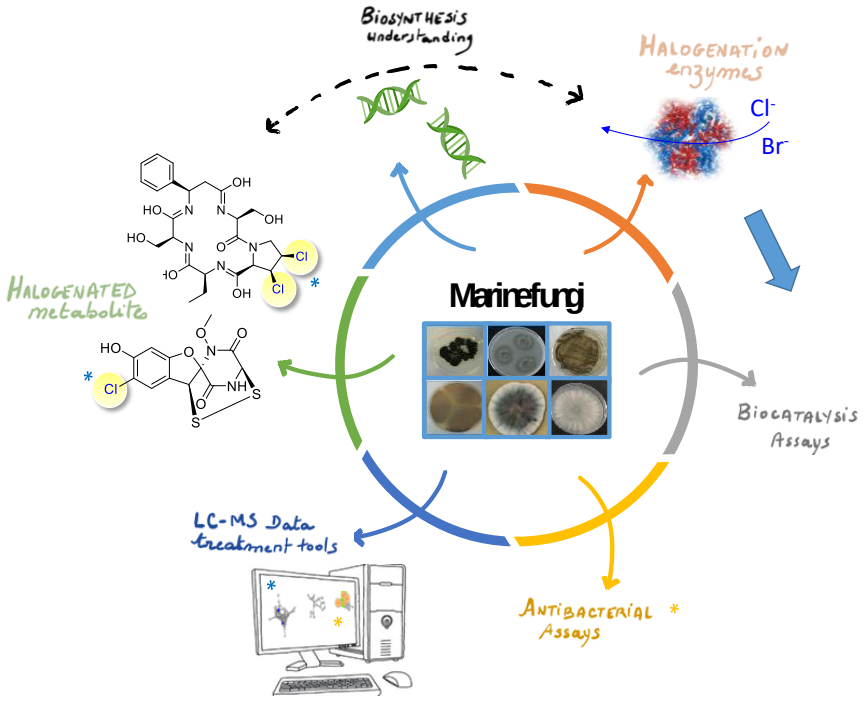

Figure 1: Overview of the HALO-CAT project (ANR-21-CE44-0003)

References: [1] Roullier *et al.*, *Anal. Chem.*, 2016, 88, 9143-9250. **[2]** Cochereau *et al.*, *Molecules*, 2022, 27, 3157. **[3]** Cochereau *et al., Marine Biotechnol.*, 2023, *in press*. **[4]** Cochereau *et al., Biocatal. Agric. Biotechnol.*, 2023, *in revision*.

Conférence 2

SYNTHESIS OF *PIPER* SPP. ALKALOIDS BY PHOTOCATALYTIC ASSEMBLIES OF PIPERINE

EVANNO LAURENT

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Piper spp. constitute a family of lianas cultivated for their edible berries used as spices. The most popular one is *Piper nigrum* which is universally consumed as the green, white and black peppers. Its pungent taste is due to piperine isolated in 1819 by Ørsted. Since 2001, several dimeric structures were isolated from *P. nigrum* and *P. chaba* (dipiperamides, nigramides, chabamides, and piperchabamides). Two dimeric patterns are encountered: i) the vinylcyclobutanes from [2+2] assemblies; ii) the cyclohexenes from [4+2] assemblies. In the vinylcyclobutane group, six molecules originates from the dimerization of piperine [dipiperamides A, B, E, F and G and nigramide R], while the other related compounds [diperamides C and D, nigramides P, Q and S, piperchabamide H] originate from cross-assemblies [mainly piperine, piperettine and ilepcimide]. In the cyclohexene group more structural diversity is encountered. Only two compounds originate from the [4+2] assemblies of piperine [chabamide and nigramide B], while others are from cross assemblies of related precursors, bearing variation on the amide function, the substitution of the polyene and the number of double bonds.

To realize the synthesis of these dimers, we decided to carry out [2+2] and/or [4+2] cycloadditions directly on piperine. To perform regioselective and diastereoselective assemblies, we turned to photocatalysis. Conditions adapted to a reductive photocatalytic cycle allowed us to exclusively activate the **α-β** double bond of piperine and to selectively obtain a set of natural products depending on the catalysts and adjuvants used.

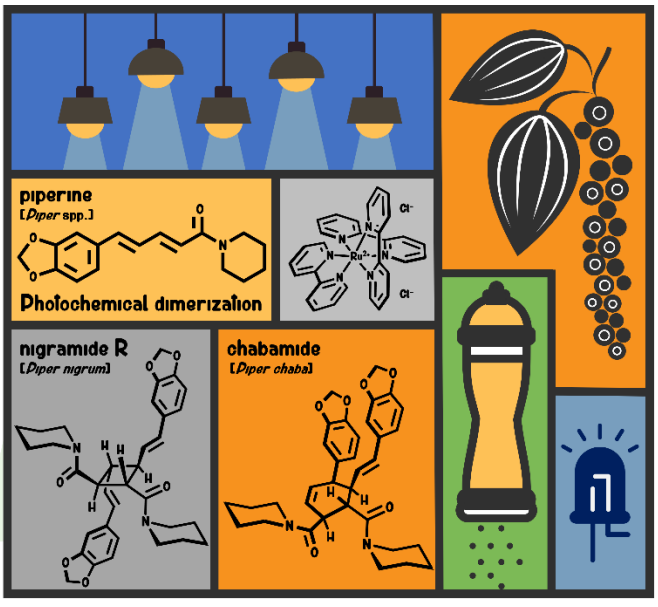

Figure 1: assemblies of piperine dimers

References: [1] T. Rukachaisirikul, S. Prabpai, P. Champung, A. Sukusamrarn. *Planta med.* 2002, *68*, 853-855. **[2]** K. Wei, W. Li, K. Koike, Y. Chen, T. Nikaido, *J. Org. Chem.* 2005, *70,* 1164-1176.

Conférence 3

EXPANDING THE PORTFOLIO OF ENZYMES FOR BIOCATALYSIS BY EXTENSIVE BIODIVERSITY SCREENING

ELISEE Eddy[1], DUCROT Laurine[1], MEHEUST Raphaël[1], STAM Mark[1], PELLETIER Eric[1], BASTARD Karine[1], PETIT Jean-Louis[1], FOSSEY-JOUENNE Aurélie[1], Adrien DEBARD Adrien[1], PELLOUIN Virginie[1], BENNETT Megan[2], de BERARDINIS Véronique[1], ZAPARUCHA Anne[1], GROGAN Gideon[2], VALLENET David[1]*, VERGNE-VAXELAIRE Carine[1]*

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[2] *York Structural Biology Laboratory, Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK.*

In an international movement of energy transition, catalysis, and more particularly biocatalysis which uses enzymes as catalysts, meets the needs of a more sustainable chemistry **[1]**. For biocatalysis to be a more applied alternative to conventional chemistry, it is essential to provide various enzyme templates in terms of sequences and structures. Even if protein engineering is a powerful method for evolving enzymes according to performance criteria, these mutants do not afford the diversity required to access the full potential of biocatalysis. The current boom in the use of (meta)genomic data from the exploration of microbial communities provides a gigantic resource of potential biocatalysts. Promoting bioinformatics approaches to efficiently identify the targeted enzyme is a major challenge.

In the course of the discovery of biocatalysts for amine production (key compounds notably in the pharmaceutical industry), interest in oxidoreductases has grown, particularly for enzymes catalyzing the NAD(P)H-reductive amination of ketones with ammonia. Previously restricted to engineered α-aminoacid dehydrogenases, this enzymatic toolbox has been recently extended by the discovery of genes coding for native AmDHs (nat-AmDHs) by our group **[2,3]**, in addition to reductive aminases and engineered ε-deaminating L-lysine dehydrogenase. Following the preliminary success of identification of other nat-AmDHs among metagenomic databases **[4]**, a deep exploration of available sequenced biodiversity has been conducted. This gave rise to an extended nat-AmDH family of 17k sequences for which representative enzyme products were experimentally tested for reductive amination activity. The exploration of their active site diversity based on an Active Site Modelling and Clustering analysis **[5]**, supported by crystallographic structures **[3,6]** and 3D-models, led to the discovery of homologs with key structural and activities variations that will be highlighted (Figure 1). These results also promote the use of bioinformatics research methods within the biocatalysis community.This work is supported by the Agence Nationale de la Recherche through the MODAMDH (ANR-19-CE07-0007) and ALADIN (ANR-21-ESRE-0021) projects.

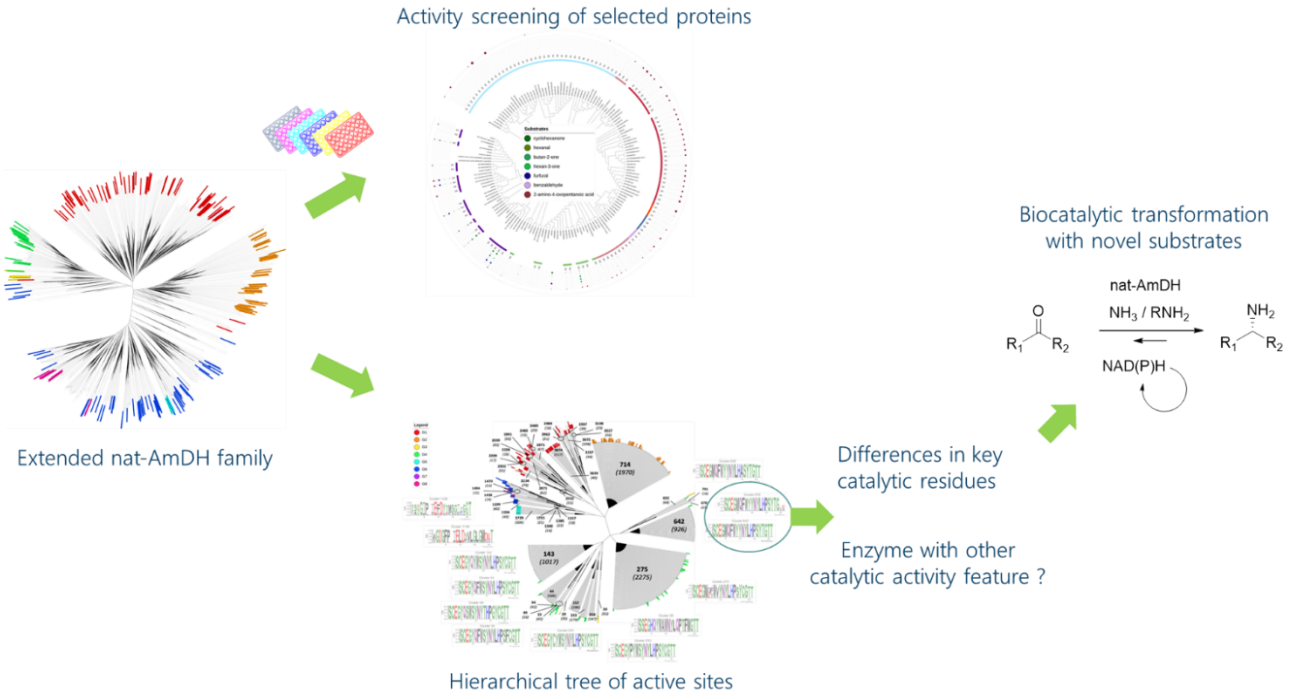

Figure 1: Identification of Amine Dehydrogenases (nat-AmDHs) within biodiversity for biocatalysis applications

References: [1] Sheldon, R. A.; Woodley, J. M., *Chem. Rev.* **2018,** *118* (2), 801-838. **[2]** Ducrot, L. et al.; *Adv. Synth. Catal.*, **2020**, *363*, 328-351. **[3]** Mayol, O. et al.; *Nature Catal.*, **2019**, *2*, 324-333. . **[4]** Caparco,A. et al.; *Adv. Synth. Catal.*, **2020**, *362*, 2427-2436. **[5]** Melo-Minardi et al., *Bioinformatics*, **2010**, 26, 3075-3082. **[6]** Bennett et al., *ChemBioChem*, **2022**, *23* (10), e202200136. and Trauner, *Angew. Chem. Int. Ed.*, 2017, 56, 12332-12335.

Conférence 4

PHYTOCHEMICAL STUDY OF ORNEMENTAL PLANTS CULTIVATED IN CENTRE-VAL DE LOIRE, FRANCE

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The Centre-Val-de-Loire (CVL) region is the leading region in the cosmetic industry and the second horticultural region in France. This production of ornamental plants generates a significant amount of biomass, which can have high potential as active ingredient for the cosmetic industry. The identification of bioactive compounds from these biomasses can lead to their valorisation as co-products in circular economy.

Several genera as *Clematis*, *Lonicera* and *Euonymus* are widely cultivated for ornament in CVL and may present a wide diversity of compounds leading in different bioactivities as antioxidant, anti-inflammatory or anti-aging activities. To identify species or even varieties produced in CVL with high potential for a cosmetic valorisation, a phytochemical study of these 3 genera was undertaken. A representative mapping of the chemical diversity that may be present in these different genera was carried out through a metabolomic study including specimens cultivated under controlled conditions in CVL but also wild specimens collected in the Botanical Garden of Fribourg and Neuchâtel which possess a large collection of species from these 3 genera.

This metabolomic study by including plant material from these different places and considering different metadata as species, localisation, culture conditions, allowed to assess parameters influencing phytochemical composition of the plant and so others metadata as their bioactivities. This correlation between phytochemistry and biological activities will make it possible to highlight active molecules and then will allow to select the most promising species for a cosmetic valorisation and to develop extraction methodologies focused on these compounds.

Conférence 5

4-PHENYLBUTYRIC ACID, A « SWISS KNIFE » MOLECULE WITH HIGH POTENTIAL IN AGRICULTURE

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The naturally occurring molecule, 4-phenylbutyric acid (4-PBA), is produced by soil and ocean bacteria that belongs to the *Bacillus* genera [1, 2]. It has widely been used in academic research for alleviating and probing endoplasmic reticulum stress [3-7], a situation encountered in eukaryotic cells when misfolded polypetides accumulate in the organelle lumen. Despite the extensive literature on the subject, the exact mode of action of 4-PBA at the molecular level still remains elusive *in vivo*. In our laboratories, we have extended those works, and found out that 4-PBA also displays an unexpected, potent fungi-toxic activity of broad spectrum [8] associated with a potential activity of plant defense stimulation (PDS) [9]. In a European context of ecological transitions where safer phytosanitary methods are needed, we believe that 4-PBA could represent a sustainable alternative to control phytopathogenic micro-organisms in the field, including fungi and oomycetes responsible for several harmful cryptogamic diseases. Our work now focusses on the elucidation of the yet-to-be deciphered molecular mechanisms underlying both the bio-fungicide and the PDS activities. This is a mandatory step towards the successful development of a biocontrol product containing the 4-PBA as active substance.

References: [1] Nithyaa *et al. Biofouling,* 2011, 27, 519-528. **[2]** Asolkar *et al.*, 2015, Patent US9084428. **[3]** Cuadrado-Tejedor *et al.*, *Curr. Med. Chem.*, 2011, 18, 5545-5553. **[4]** He and Moreau R, *Pharmacol. Res.*, 2019, 144, 116-131. **[5]** Watanabe and Lam, *J. Biol. Chem.*, 2008, 283, 3200-3210. **[6]** Yang *et al.*, *Plant J.*, 2016, 85, 83-95. **[7]** Mai *et al.*, *FEMS Yeast Res.*, 2018, 18. **[8]** Vasselon *et al.*, 2020, Patent FR 20 05221, WO2021/233961. **[9]** Cacas and Champion, 2012, Patent FR2 993 141, WO2014/009402.

Conférence 6

CANNABIS SATIVA – VARIATIONS AUTOUR D'UN THEME

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Conférence 7

FINDING NEEDLES IN A HAYSTACK FASTER AND MORE ACCURATELY? PROPOSED WORKFLOWS COMBINING CHEMOMETRICS AND DEREPLICATION BASED ON BOTH MS AND ^{13}C NMR

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Due to the propensity of natural products (NPs) to interact with targets of therapeutic or agronomic interest, some NPs chemists focus on the identification of bioactive compounds in complex matrices (*i.e* plant or microorganism extracts). To avoid the repetitive isolation of previously described NPs and time-consuming bioassay guided fractionation strategies, the early-on identification of active metabolites from complex mixtures has become a key element in NPs research.

In this regard, **chemometrics[1]** are an effective way to spot bioactive NPs. Conventionally, Ultra High-Performance Chromatography (UPLC) coupled with High Resolution Mass Spectrometry (HRMS) is used for chemical profiling. These results are then combined with biological data allowing the identification of bioactivity markers. The latter are usually selectively isolated for full spectral characterization and high confidence identification. Despite its indubitable assets, UPLC-HRMS encounters certain limitations related to the solvents that can be used, the time required to set up chromatographic conditions, the ionizability of analytes or the differentiation of (stereo)isomers.

As an alternative to isolation for full structural determination, **early annotation** of selected NPs can be performed by MS or NMR. This direct and rapid approach is based on algorithms that compare the acquired spectral data with those of metabolites reported in a given database (DB). Finally best scores are assigned to the most appropriate structural proposals. These strategies either use experimental MS² [e.g. Global Natural Product Social (GNPS)] / NMR (e.g. NP-MRD) repositories**[2–4]** or *in silico* DBs. Indeed, even if the collection of experimental NMR**[3,4]** and MS**[5–8]** data has started, it is a huge task that requires a continuous and collective effort. Alternatively, DBs of computationally generated *in silico* spectra are becoming more and more important with respect to the constant progress of spectral prediction algorithms and software [e.g. CFM-ID4, MetFrag, ACD/NMR Predictors (C and H), nmrshiftdb2]. Consequently, the use of DBs containing the predicted fragmentation spectra or ^{13}C-NMR chemical shifts (δ_C) of NPs allows relevant structural assumptions to be made today. This step, which can be described as the **dereplication** of a complex mixture (i.e. unambiguous identification of the known NPs responsible for the activity of an extract) is therefore now widely used.

While MS is one of the most widely used methods, ^{13}C-NMR, albeit less sensitive, permits the differentiation of (stereo)isomers, which is a significant advantage. As modern NMR spectrometers provide useful data sets in a reasonable amount of time, we have developed and made available free of charge a dereplication software based on ^{13}C-NMR analysis.**[9,10]** **MixONat** (https://sourceforge.net/projects/mixonat/) processes ^{13}C data as well as DEPT 135 and 90 data, allowing filtering by carbon type (i.e. CH_3, CH_2, CH and C) as well as by molecular weight. It has been shown to be effective in identifying NPs with a good level of confidence, including using predicted chemical shift (δ_C) DBs.**[11–13]**

As many NPs show very close structural similarities to the molecules used in matrices (e.g. xanthones) during matrix-assisted laser desorption ionization (MALDI), they can be easily ionized without matrix support. In this respect, laser desorption ionization coupled with matrix-free HRMS (**LDI-HRMS**) has shown comparable results to LC-MS **[14,15]**. A notable benefit is that LDI-MS experiments can be performed in seconds.

Since NMR and MS are complementary **[16]**, we propose two workflows that combine chemometrics and dereplication based on both MS and ^{13}C NMR to identify bioactive NPs directly in the mixture.

In a first workflow, a holistic chemometric approach using LDI-MS assisted by ^{13}C NMR is applied for the early and rapid identification of anti-AGEs NPs (ability to prevent the formation of advanced glycation end products) from crude extracts of *Garcinia parvifolia* bark, known to contain xanthones.**[17]**

A second workflow proposes the selection of metabolites of interest using $HRMS^2$ and a bioactivity-based molecular network (MN) **[18]** using chemometrics results [i.e., Variable Importance of Projection (VIP) score and Regression Coefficient (RC) from PLS model]. Annotation is then performed using the *in silico* fragmenter MetFrag included in the Progenesis QI software, ^{13}C-NMR based dereplication of fractions using the freely available MixONat software and chemotaxonomically based DBs of NPs including their predicted δ_C.

References: [1] Kellogg, J. J. *et al. J. Nat. Prod.* 2016, *79* (2), 376–386. **[2]** Wang, M. *et al. Nat Biotechnol* 2016, *34* (8), 828–837. **[3]** Wishart, D. S. *et al. Nucleic Acids Res.* 2022, *50* (D1), D665–D677. **[4]** Kuhn, S. *et al. Magn. Reson. Chem.* 2021, *59* (8), 792–803. **[5]** Fox Ramos, A. E. *et al. Sci Data* 2019, *6* (1), 15. **[6]** Olivier-Jimenez, D. *et al. Sci Data* 2019, *6* (1), 294. **[7]** Vargas, F. *et al. Rapid Commun. Mass Spectrom.* 2020, *34* (10), e8725. **[8]** Agnès, S. A. *et al. Sci Data* 2022, *9* (1), 270. **[9]** Bruguière, A. *et al. Anal. Chem.* 2020, *92* (13), 8793–8801. **[10]** Bruguière, A. *et al. Planta Med. 2021, 87* (12/13), 1061–1068. **[11]** Silva-Castro, L. F. *et al. Phytochem. Anal.* 2021, *32* (6), 1102–1109. **[12]** Azonwade, F. *et al. Phytochem. Anal.* 2023, In press. **[13]** Yin, T. *et al. J. Food Compos. Anal.* 2023, *115*, 104975. **[14]** Schinkovitz, A. *et al. Anal. Bioanal. Chem.* 2018, *410* (24), 6187–6195. **[15]** Le Pogam, P. *et al. Anal. Bioanal. Chem.* 2020, *412* (27), 7405–7416. **[16]** Wolfender, J.-L. *Anal. Chem.* 2019, *91* (1), 704–742. **[17]** Meunier, M. *et al. Talanta* 2023, *253*, 123998. **[18]** Nothias, L.-F. *et al. J. Nat. Prod.* 2018, *81* (4), 758–767.

Conférence 8

CHEMISTRY OF ENDOPHYTIC FUNGI: NATURE, ECOLOGICAL ROLES AND APPLICATIONS

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Most of the plants in natural and anthropogenic ecosystems are colonized by unapparent and symptomless microorganisms (bacteria and fungi) called endophytes. Indeed, endophytes are invading the living tissues of the host plant without causing any symptom of disease. Endophytic fungi establish mutualistic associations with their host plants conferring fitness benefits such as tolerance to biotic and abiotic stresses. These abilities make them particularly interesting for the study of such biological phenomenon.
The molecular mechanisms providing such protection are still poorly understood. However, various metabolites involved in these interactions within the plant microbiota as well as with their host are increasingly suspected.

By using multidisciplinary approaches combining chemistry of natural products and fungal genetics, we will provide new insights in the ecological roles of the endophytes in marine and terrestrial environments and point out the key role of the molecular dialogue. We will also demonstrate that deciphering this chemical communication is a way to identify widely diverse and original compounds displaying potent biological activities especially in regard with agrochemical and life science applications.

Conférence 9

BIOMIMETIC NATURAL PRODUCT SYNTHESIS

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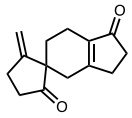
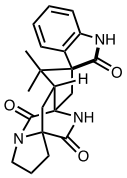
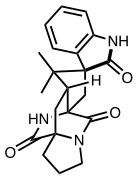
Our research effort is primarily focused on the total synthesis of natural products, exploring new strategies and concepts in chemical synthesis, and developing new synthetic methodology. This presentation will be an account of our research into how molecular complexity is rapidly and selectively generated in biosynthetic pathways. This will include our development of new synthetic strategies towards complex natural products (see completed targets below) and the exploration of new concepts in asymmetric synthesis.



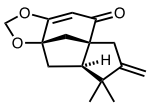
ulodione A
2 steps
Angew. Chem. Int. Ed. **2022**, e202207004



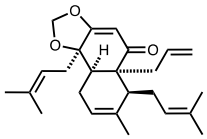
brevianamide X
8 steps
Chem. Sci. **2022**, *13*, 1313–1322



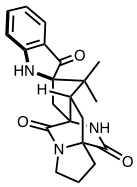
brevianamide Y (& Z)
7 steps
Chem. Sci. **2022**, *13*, 1313–1322



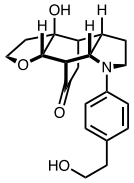
tricycloillicinone
5 steps (formal)
Org. Lett. **2021**, *23*, 3248–3252



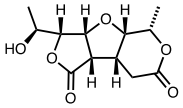
cycloillicinone
4 steps
Org. Lett. **2021**, *23*, 3248–3252



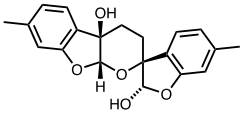
brevianamide A (& B)
7 steps
Nat. Chem. **2020**, *12*, 615–619



incargranine A
4 steps
Org. Biomol. Chem. **2019**, *17*, 1698–1702



angiopterlactone B
4 steps
Org. Lett. **2017**, *19*, 2199–2201



thymarnicol
6 steps
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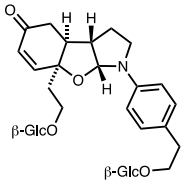

millingtonine
7 steps
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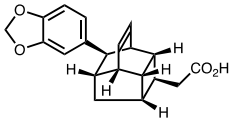
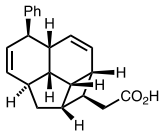
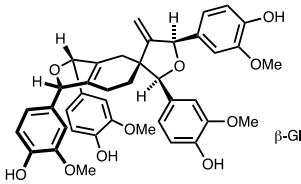


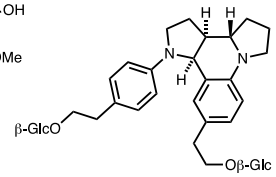
kingianic acid E
8 steps
Chem. Sci. **2015**, *6*, 3886–3890



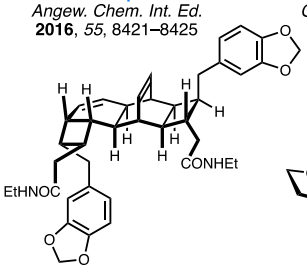
endiandric acid A
8 steps
Chem. Sci. **2015**, *6*, 3886–3890



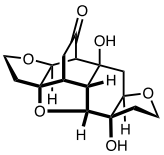
ramonanin A (B-D)
7 steps
Angew. Chem. Int. Ed. **2015**, *54*, 1795–1798



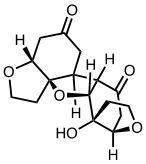
incargranine B
6 steps
Angew. Chem. Int. Ed. **2013**, *52*, 13273–13275



kingianin A (D & F)
10 steps
Angew. Chem. Int. Ed. **2013**, *52*, 4221–4224



incarvilleatone
4 steps
Org. Lett. **2012**, *14*, 4537–4539



incarviditone
4 steps
Org. Lett. **2012**, *14*, 4537–4539

Conférence 10

QUALITATIVE METABOLOMICS FOR PHENOTYPING OF NATURAL PRODUCTS BIOTRANSFORMATION

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Biotransformation, a synonymous term of metabolism, is an underestimated but important part of natural product-based drug discovery. Many natural products undergo biotransformation by gut microbes and liver enzymes when taken orally. As the metabolites will have beneficial and adverse effects different from those of the precursor compounds, understanding of the metabolic dynamics will expand our knowledge on the pharmacology of various natural products. Besides, microbial biotransformation of plant or animal metabolites has been an important source of natural products since the ancient invention of wine and cheese. Current advances in biocatalyst-driven synthesis are increasing the potential value and applicability of microbial biotransformation in drug discovery.

Biotransformation is technically difficult to investigate. We have been able to observe only a limited portion of the metabolic space; however, recent advances in mass spectrometry-based untargeted metabolomics paved up our way to observe the chemistry of natural product biotransformation. Metabolite mining techniques, such as spectral similarity networking, are the major key advances enabling qualitative analysis on the complex mixtures **[1]**. Here, I will highlight the applicability of mass spectrometry-based qualitative metabolomics for observation on the different types of biotransformation. Computational mass spectrometry-based metabolite mining **[2]** will enable us target-based screening of molecules biotransformed by gut microbes and liver enzymes by being integrated with native metabolomics **[3]**. Metabolomics-based catalytic phenotyping can accelerate discovery of microorganism-derived biocatalysts when integrated with genomics and transcriptomics, of which a proof-of-concept study led us to discover a previously unknown UDP-glycosyltransferase, designated UGT66A1, which is an enzyme catalyzing O-xylosylation on many different structural scaffolds having phenolic OH groups.

References: [1] Beniddir *et al., Nat. Prod. Rep.*, 2021, 38, 1967–1993. **[2]** Yu *et al.*, *Anal. Chem.*, 2022, 94, 1456–1464. **[3]** Reher *et al.*, *Nat. Commun.*, 2022, 13, 4619.

Conférence 11

GENOME MINING PIPELINES AND TOOLS TO GUIDE THE DISCOVERY OF NEW NATURAL PRODUCTS

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Next-generation sequencing methods have made sequencing faster, cheaper, and easier than ever and have revolutionized almost every field of biology. The constantly growing volume of DNA sequence data has made genome mining an important tool for the detection and prediction of promising secondary metabolites and has led to a renaissance in natural product-based drug discovery. Thousands of putative gene clusters are available in public databases, the challenge being now to triage the most promising pathways to guide laborious wet-lab experiments, assist with the dereplication of already known compounds, and predict interesting bioactivities based on genomic data.

Here we introduce a selection of computational tools and methods developed by the Ziemert lab, which facilitate genome mining efforts for bioactive secondary metabolites and can be used for rapid automated identification and examination of novel biosynthetic gene clusters.

EVALUATION DE LA GENOTOXICITE DES PRODUITS DE PHYTOTHERAPIE

NESLANNY Fabrice
Groupe ERBC

Parmi les différentes formes d'utilisation des plantes médicinales, on retrouve les extraits de plantes ainsi que les poudres de plantes qui sont des mélanges complexes.

La Directive 2004/24/CE relative aux médicaments traditionnels à base de plantes requiert en outre de fournir une documentation démontrant l'innocuité du produit concerné dans les conditions d'emploi spécifiées.

Concernant précisément l'évaluation non clinique des médicaments à base de plantes (EMEA/HMPC/32116/2005), avec la description des caractéristiques botaniques et phytochimiques de

Une documentation toxicologique correspondant en une revue de la littérature scientifique et/ou en la mise en œuvre d'études expérimentales qui intègre systématiquement l'évaluation du potentiel mutagène (mais plus rarement la réalisation d'études de cancérogenèse et/ou de toxicité pour la reproduction et la fertilité), est réalisée.

Lorsqu'il est nécessaire de produire des données expérimentales, la 1ère étape consiste ainsi en la réalisation d'un test d'induction de mutations géniques sur système bactérien, i.e., le test d'Ames (OCDE 471).

En cas de résultat clairement négatif dans le test d'Ames, aucun autre test de génotoxicité n'est exigé, la mutagenèse n'étant plus un potentiel paramètre limitant. En revanche, en cas de réponse équivoque ou positive, différentes hypothèses et de multiples scénarii sont possibles selon que l'origine de l'activité génotoxique est clairement identifiée et donc attribuée à un (ou des) constituants spécifiques ou non. Ainsi, l'implication de la présence de molécules ubiquitaires, ou spécifiques est évaluée.

Cette présentation portera donc sur la présentation succincte de la réglementation de l'évaluation de la génotoxicité des substances végétales, des stratégies qui peuvent être suivies. Elle sera agrémentée de nombreux exemples publiés et originaux permettant de suivre le logigramme expert qui s'apparente parfois à un parcours du combattant, qui finalement, peut finir dans une impasse…

Conférence 13

FROM CHÂTENAY-MALABRY TO ORSAY: AN ODYSSEY INTO 60 YEARS OF PHYTOCHEMISTRY

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Since its creation in the late 1960s, plant metabolites pertaining to various structural series have been continuously isolated in our laboratory. Although most of these phytochemical campaigns had been geared towards the isolation and structure elucidation of new isoquinoline alkaloids, and monoterpene indole alkaloids to a lesser extent, the laboratory collection encompasses more than 800 different chemical entities that spread across a much wider variety of scaffolds and that comprise seemingly unique entries, *viz*. that had not been isolated nor synthesized elsewhere since their initial report in Châtenay-Malabry. This communication aims at presenting some of the patrimonial-themed research activities carried out in the laboratory within the very last few years. A first part of this presentation will introduce the efforts made to upload MS/MS data related to structurally homogeneous phytochemicals to the GNPS repositories, and that led to implement different databases out of our collections from 2019 to 2022 **[1,2]**. During the curation of these data, it appeared that some specific compounds deserved a spectroscopic reassessment as doubts existed as to the validity of their structure (based on biosynthetic concerns **[3]** or inconsistencies between the spectroscopic data of the natural isolate with that of the synthetic purported structure **[4]**) or to identify the correct structure when the literature comprises several, conflicting chemical depictions for a single natural product **[5,6]**. Different recent investigations from our research team will be used to illustrate different scenarios that could give rise to such structural reassessments. In each of these cases, holding the original sample provided us with a unique opportunity to dispel these structural doubts, especially when considering that the spectroscopic data published in the 1970s would have often been too scant to enable a proper structure revision on their own. A final example will emphasize the connections between our collections of natural products and the current phytochemical investigations carried out in the lab through the molecular-networking based investigation of *Callichilia inaequalis* (Apocynaceae). In this latter case, locating the original sample of the monoterpene bisindole alkaloid criophylline not only enabled a firm validation of its core structure but could also support the structure elucidation of some newly isolated derivatives, including the first-ever reported sulfated monoterpene indole alkaloid: 14'-*O*-sulfocriophylline **[7]**. Such revisions and structural clarifications occur between 38 and 64 years after the initial description of the products.

References: **[1]** Fox Ramos *et al.*, *Sci. Data*, 2019, 6, 15; **[2]** Agnès *et al.*, *Sci. Data*, 2022, 56, 12332-12335; **[3]** Kouamé *et al.*, *Org. Lett.*, 2021, 23, 5963-5968 ; **[4]** Jagora *et al.*, *J. Nat. Prod.*, 2021, 23, 5963-5968 ; **[5]** Retailleau *et al.*, *Metabolites*, 13, 470 ; **[6]** Beniddir *et al.*, *Phytochemistry*, 2023, *in press* ; **[7]** Otogo N'Nang *et al.*, *J. Nat. Prod.*, 2023, *in press*.

Conférence 14

CHEMISTRY OF NATURAL PRODUCTS AND METABOLOMICS APPLIED TO ARCHAEOMETRY AND CULTURAL HERITAGE CHEMISTRY

Gérald CULIOLI [1]

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The analysis of organic residues from archaeological artefacts can answer many archeological questions **[1]**. Nevertheless, the amorphous nature of these organic materials does not allow them to be characterized by morphological approaches such as those used for other types of samples (wood fibers, textiles, pollens, seeds…). In this particular context, resinous materials are remnants of the past that may contain well-preserved organic chemomarkers. In some cases, these chemical markers allow to trace the botanical origin of natural resins used for utilitarian or ritual purposes and, more broadly, to better explore the diverse and complex ancestral practices linked to such raw materials, or to obtain valuable information about trade routes and exchanges **[2]**. In the field of cultural heritage science dedicated to the study of easel or wall paintings, the analysis of the wide range of organic substances used by artists (oils, proteins, gums, waxes, resins ...) is fundamental in order to better understand the techniques used in the creation of these paintings and to determine the most appropriate methods of restoration and/or conservation **[3]**. Another area of cultural heritage chemistry deals with natural organic dyes used since the dawn of time to color natural fibers. Physicochemical analyses dedicated to this type of samples are challenging and must compensate for the low concentrations of dyes and the complex mixtures present in historical textiles, as well as the degradation of both dyes and textiles **[4]**.

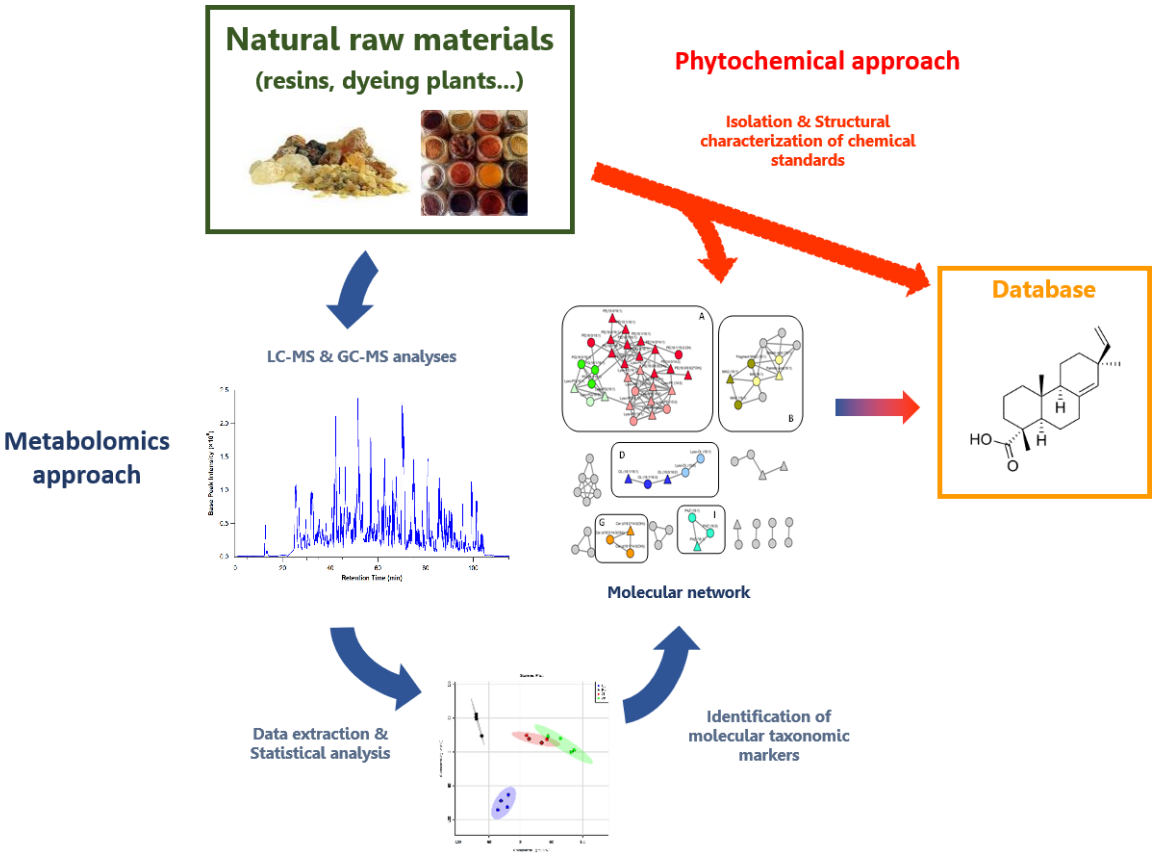

Figure 1: Analytical workflow dedicated to the characterization of molecular taxonomic markers in the field of archaeometry and cultural heritage chemistry.

Ultimately, studies aiming at characterizing organic molecules in archaeological and cultural heritage contexts require the use of efficient analytical techniques to detect the presence of specific molecular markers found in very low amounts in very complex and degraded samples.
In recent years, metabolomics – the latest of the so-called "omics" sciences – has emerged as an approach of choice to characterize the whole set of low molecular weight organic molecules in complex samples. The very rapid progress in this field has been made possible thanks to the joint technological advances of mass spectrometry and bioinformatics **[5]**. Moreover, the LC-MS based molecular networking allows to optimize the annotation process **[6]** and new and very original tools are being developed to increase the capabilities of molecular networks (See **[7]** for a review).

In this context, this presentation aims to show the great potential of metabolomics and molecular networking applied to archaeological and cultural heritage samples in order find taxonomical and degradation molecular markers, mainly from natural resins and dyeing plants. The purpose of such work is to provide clues (i) to archaeologists, to better understand ancient practices and recipes, and (ii) to restorers and museum curators, to allow them a better restoration/conservation of cultural heritage objects.

References: **[1]** Evershed *Archaeometry*, 2008, 50, 895-924. **[2]** Regert *et al. Archaeometry*, 2008, 50, 668-695. **[3]** Geddes da Filicaia *et al. Analytica Chimica Acta*, 2023, 1246, 340575. **[4]** Tamburini *Dyes and Pigments*, 2019, 163, 454-474. **[5]** Patti *et al. Nature Reviews Molecular Cell Biology*, 2014, 13, 263-269. **[6]** Aksenov *et al. Nature Biotechnology*, 2021, 39, 169-173. **[7]** Beniddir *et al. Natural Product Reports*, 2021, 38, 1967-1993.

Conférence 15

TRACING SPONGE SPECIALIZED EXOMETABOLITES IN SEAWATER SHEDS NEW LIGHT ON THEIR CHEMICAL DIVERSITY

MAUDUIT Morgane,[1] GRENIER Marie,[1] DERRIEN Marie,[1] GREFF Stéphane,[1] MOLINARI Sacha,[1] CHEVALDONNE Pierre,[1] PEREZ Thierry,[1] SIMMLER Charlotte* [1]

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In the Mediterranean Sea, species assemblages of coralligenous habitats are dominated by sponges.[1] These sessile marine holobionts are known to produce a plethora of structurally diverse specialized metabolites that are part of their toolbox for defense, growth and communication strategies.[2] Through their metabolic activities involving their microsymbionts, sponges may release part of their metabolites, hence termed exometabolites (EMs). Such EMs can be rapidly diluted, possibly bio-transformed, and added to a pool of other marine metabolites, thereby defining a complex chemical seascape. Individually or collectively, these EMs can serve as nutrients or be perceived as cues sustaining communication between organisms.[3] An overarching goal but also challenge for marine chemical ecologists is to be able to decipher, within the chemical seascape, molecular signatures that are involved in target species interactions.[3-5] This presentation will showcase complementary methodologies designed to enrich EMs from seawater around different sponge species (and other benthic invertebrates) and characterize their specialized EMs in a rather dense mixture of seawater metabolites.[6,7] The overall collected results will illustrate how studying sponges' specialized EMs sheds new light on their already well studied chemical composition, while offering perspectives of research in marine chemical ecology.

References: **[1]** Grenier, M. *et al.* Zootaxa **2018**, 4466 (1), 205. **[2]** Puglisi, M. P *et al.* Nat. Prod. Rep. **2019,** 36 (3), 410–429. **[3]** Hay, Mark E. Annu. Rev. Mar. Sci. **2009**, 193–212. **[4]** Saha, M. *et al.* Front. Ecol. Environ. **2019**, 17 (9), 530–537. **[5]** Santonja, M. *et al*. Mar. Biol. **2018**, 165 (7), 1–15. **[6]** Mauduit, M. *et al.* ACS Omega **2022**, 7 (47), 43068–43083. **[7]** Mauduit, M.; Derrien M.; Grenier M.; *et al.* submitted to Nat. Commun. **2023**.

Conférence 16

ANTI-INFLAMMATORY Ω-OXIDIZED TOCOTRIENOLS MODULATING THE ARACHIDONIC ACID METABOLISM

ALSABIL Khaled[1], VIAULT Guillaume[1], SERAPHIN Denis[1], RICHOMME Pascal[1], WERZ Oliver[2], KOEBERLE Andreas[3], HELESBEUX Jean-Jacques[1,*]

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Inflammation is an adaptive response of the immune system triggered by exogenous harmful stimuli or damaged tissues to maintain homeostasis of the body [1]. This process is also involved in the development of various pathologies, e.g. asthma, cardiovascular diseases, some types of cancer, and metabolic disorders [2-3]. Inflammatory lipid mediators play a key role in the cascade response including the accumulation of leukocytes and the leakage of plasma from small vessels to inflamed tissues. 5-Lipoxygenase (5-LOX)-derived leukotrienes (LTs) represent a class of pro-inflammatory lipid mediators derived from arachidonic acid (AA) [4]. 5-LOX, a non heme iron-containing dioxygenase, is the key enzyme in LT biosynthesis that catalyses the oxidation of AA at C-5 position, yielding the intermediate (S)-5-hydroperoxyeicosatetraenoic acid (5-HPETE), and its dehydration to leukotriene A4 (LTA4) [5].

Due to the importance of LTs in the pathogenesis of inflammation-related diseases, 5-LOX has been identified as a key target for the development of new therapeutics [6]. In the frame of the Drugs from Nature Targeting Inflammation (DNTI) program, δ-amplexichromanol and δ-garcinoic acid (Figure 1) were identified as efficient inhibitors of this enzyme [7-8]. Based on these first results, a library of ω-oxidized tocotrienols was semisynthesized and evaluated. This work has allowed a better understanding of the SAR of this class of derivatives, with α-amplexichromanol as a lead from this series [9].

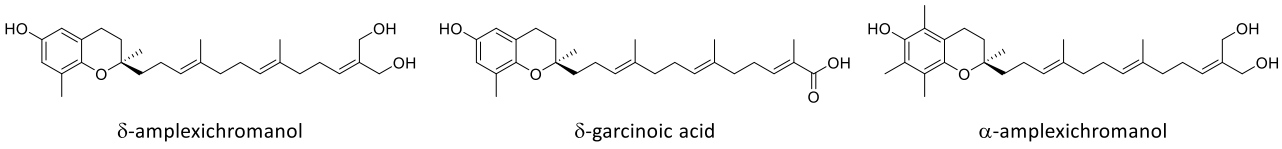

Figure 1: Typical derivatives from the ω-oxidized tocotrienol series

References: [1] R. Medzhitov, *Nature*, 2008, 454, 428-435. **[2]** G.K. Hansson, *N. Engl. J. Med.*, 2005, 352, 1685-1695. **[3]** A. Mantovani *et al.*, Cancer-related inflammation, *Nature*, 2008, 454, 436-444. **[4]** B. Samuelsson *et al.*, *Science*, 1987, 237, 1171-1176. **[5]** O. Rådmark *et al.*, *Biochim. Biophys. Acta Mol. Cell Biol. Lipids*, 2015, 1851, 331-339. **[6]** O. Werz and D. Steinhilber, *Pharmacol. Ther.*, 2006, 112, 701-718. **[7]** P. Richomme *et al.*, 2017. WO 2017/032881 A1. **[8]** K. Alsabil *et al.*, *Planta Med.*, 2016, 82, 1110-1116. **[9]** K. Neukirch *et al.*, *J. Med. Chem.*, 2021, 64, 11496-11526.

Conférence 17

HARNESSING PLANT METABOLIC DIVERSITY FOR FOOD AND HEALTH APPLICATIONS

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Plants produce a wealth of natural products. The vast majority of the natural product diversity encoded by plant genomes remains as yet untapped. The explosion in plant genome sequence data, coupled with affordable DNA synthesis and new DNA assembly technologies, now offer unprecedented opportunities to harness the full breadth of plant natural product diversity and generate novel molecules in foreign hosts using synthetic biology approaches. The recent discovery that genes for the synthesis of different kinds of natural products are organised in biosynthetic gene clusters in plant genomes opens up opportunities for mining for new pathways and chemistries. This advance, in combination with powerful new transient plant expression technology, is enabling the development of rational strategies to produce known and new-to-nature chemicals tailored for food, health and other industrial applications. This presentation will focus on our work on developing a translational synthetic biology pipeline for rapid preparative access to plant natural products and novel analogs using synthetic biology approaches. It will also highlight recent advances in our understanding of the genomic rearrangements underpinning the formation of new plant biosynthetic gene clusters, and of the functions of plant natural products in nature.

Communications courtes : résumés

Lundi 17 juillet – *session communications courtes 1*

1	11h15-11h30	**Manon MEUNIER**	Matrix-free laser desorption ionization ion mobility mass spectrometry: A complementary approach to chemometrics in natural products research
2	11h30-11h45	**Olivier BONNET**	Identifications of minor and major metabolites from plants of *Strychnos* genus using molecular networking
3	11h45-12h	**Ramla SAHLI**	Introducing natural deep eutectic solvents in Arizona solvent systems for sustainable use of centrifugal partition chromatography
4	12h-12h15	**Nangouban OUATTARA**	Etude biologique et phytochimique de plantes médicinales antimicrobiennes de Côte d'Ivoire pour une valorisation thérapeutique contre *Toxoplasma gondii*
5	12h15-12h30	**Blandine AKENDENGUE**	Antifungal activity of *Petersanthius macrocarpus* (P.Beauv.) Liben trunk bark (Lecythidaceae)

Lundi 17 juillet – *session communications courtes 2*

6	16h-16h15	**Grégoire AUDO**	Natural products purification by CPC-MS
7	16h15-16h30	**Anne-Sophie PAGUET**	Multiblock comparison of hop chemistry and its aromatic influence after brewing
8	16h30-16h45	**Thomas CHARPENTIER**	Natural Products Targeting the Unfolded Protein Response (UPR) as a New Biocontrol Strategy
9	16h45-17h	**Lúcia MAMEDE**	Profiling plants with antimalarial blood stage activity using metabolomics: An added dimension to drug discovery
10	17h-17h15	**Elvis OTOGO N'NANG**	Identification of tropical plant immune regulatory molecules inducing Mtb intracellular killing within infected macrophages to shorten TB therapy
11	17h15-17h30	**Sufi DESRINI**	Le séneçon en arbre et la renouée du Japon, des plantes invasives à potentiel anti-biofilm et antifongique

Mardi 18 juillet – *session communications courtes 3*

12	11h30-11h45	**Emie GROPPI**	OSMAC approach applied to mycotoxins production by *Fusarium verticillioides*
13	11h45-12h	**Axel LEBLOND**	Deep Chemical Exploration of Baldwin and Whitehead Biosynthetic Hypothesis for Manzamine Alkaloids Enabled by Data Science
14	12h-12h15	**Guillaume HAMION**	L'acide bétulinique, un composé naturel prometteur contre les biofilms inter-règnes
15	12h15-12h30	**Olivier BERRY**	Isolation of physiological regulators of *Prorocentrum lima* from associated fungus *Aspergillus pseudoglaucus*

Communication 1

MATRIX-FREE LASER DESORPTION IONIZATION ION MOBILITY MASS SPECTROMETRY: A COMPLEMENTARY APPROACH TO CHEMOMETRICS IN NATURAL PRODUCTS RESEACH

MEUNIER Manon[1], BREARD Dimitri[1], AWANG Khalijah[2], HAACK Martina[3], AWAD Dania[3], BRÜCK Thomas[3], DERBRE Séverine[1*], SCHINKOVITZ Andreas[1*]

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The chemical profiling of complex mixtures of isomers is a major challenge in analytical chemistry and is usually facilitated by LC-MS. In recent years, matrix-free desorption ionization mass spectrometry (LDI-MS) has emerged as a highly efficient and useful complement to LC-MS, particularly in NP research[1–3]. In contrast to LC-MS, the method requires very little sample preparation, provides immediate results, and can use any volatile solvent. Despite these advantages, the lack of chromatographic separation remains a major limitation of LDI-MS, especially for the analysis of isomers. With this in mind, a hyphenated LDI-ion mobility (IM)-MS/MS approach is presented for the differentiation of constitutional xanthone isomers from *Garcinia parvifolia*. Compound specific drift times, expressed as collision cross section (CCS) values, were evaluated, and used to augment standard LDI-MS data.

References: [1] Schinkovitz, A. et al., *Anal. Bioanal. Chem.* **2018**, *410* (24), 6187–6195. **[2] L**e Pogam, P. *et al*, *Anal. Chem.* **2015**, *87* (20), 10421–10428. **[3]** Meunier, M. et al, *Talanta* **2023**, *253*, 123998.

Communication 2

ISOLATION AND IDENTIFICATION OF SPECIALIZED METABOLITES FROM *STRYCHNOS* SPECIES USING MOLECULAR NETWORKING

BONNET Olivier[1], BENIDDIR Mehdi A.[2], CHAMPY Pierre[2], LEROY Charline[1], KAGISHA Védaste[1,3], NYIRIMIGABO Alain[1,3], HAMANN Carla[1], JGERENAIA Giorgi[1,4], LEDOUX Allison[1], TIABOU TCHINDA Alembert[1,5], ANGENOT Luc[1], FRÉDÉRICH Michel[1]

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For over two centuries [1], plants of the *Strychnos* genus, including approximately 200 species and belonging to the Loganiaceae family [2], were studied in depth for their varied therapeutic properties (e.g. treatments for fever, snakebites and stomach aches [3]), as well as for their tetanizing and curarizing properties [4]. However, this genus, so rich in promising bioactive metabolites, has not yet revealed its full phytochemical content. To this end, as part of my research project, the molecular networking workflow [5], described in the Figure 1, was applied to explore the phytochemical contents of 44 crude extracts from 28 *Strychnos* species,to unveil known metabolites not yet described in some species as well as to detect and identify unknown molecules active against malaria in various species, including *S. longicaudata* trunk barks, and *S. usambarensis* leaves.

Strychnine, a well-known metabolite of the genus, was identified by molecular networking in 7 species not yet described as strychnine producers in the literature. These identifications were confirmed using a varietyof techniques, including TLC, HPLC, NMR, MS, and MS/MS [6].

The dichloromethane extract of *S. longicaudata* trunk barks, despite showing a promising antiplasmodial activity (4.94 ± 2.51 µg/mL for the chloroquine-sensitive 3D7 strain of *Plasmodium falciparum*), was few studied to date. The purifications led us to identify alstonine as the extract's major metabolite. The antiplasmodial activity observed for alstonine was moderate (19.0 ± 5.28 µM for chloroquine-sensitive 3D7 strain of *Plasmodium falciparum*) and, therefore, it does not explain the initial activity. Further purifications are therefore in progress to identify the other unknown metabolites.

Finally, the exploration of the alkaloidic extract content from antiplasmodial leaves of *S. usambarensis* [7] revealed the presence of minor alkaloids with *m/z* masses superior to 900 (for example, 943.8 *m/z*, and 944.4 *m/z*). To our knowledge, such a mass was never described previously in the literature for an alkaloid isolated from *S. usambarensis*. Therefore, purifications were performed using open column, and preparative and analytical HPLC techniques. NMR and MS/MS analyses provided us interesting structural information on themetabolite with a mass of 944.4 *m/z*. Future purifications and analyses will enable us to confirm the structure.

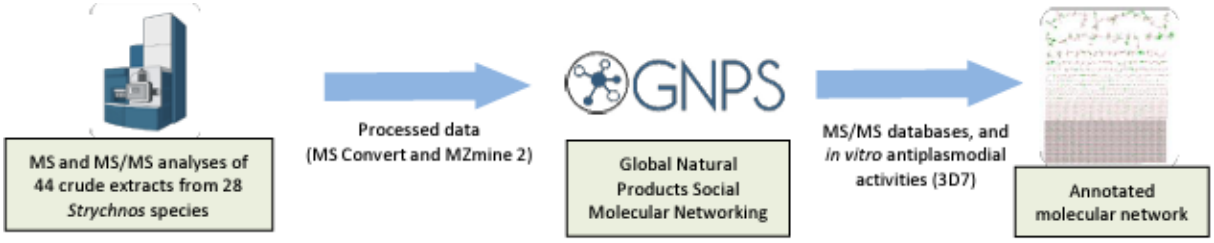

Figure 1: Workflow applied for exploring the phytochemical content of *Strychnos* crude extracts.

References: **[1]** Angenot, Mémoire en Sciences Pharmaceutiques, Université de Liège, Liège, 1974-1976. **[2]** World Flora Online (2023). *Strychnos* L. Available at: http://www.worldfloraonline.org/taxon/wfo-4000036956 (Accessed June 11, 2023). **[3]** Dr. Duke's Phytochemical and Ethnobotanical Databases, US Dpt of agriculture. Available at: https://phytochem.nal.usda.gov/phytochem/search/list (Accessed June 11, 2023). **[4]** Philippe *et al.*, Toxicon, 2004, 44, 405-416. **[5]** Fox Ramos *et al.*, Nat. Prod. Rep., 2019, 36,960-980. **[6]** Bonnet *et al.*, Toxicon, 2022, 215, 57-68. **[7]** Bonnet *et al.*, Front. Mol. Biosci., 2022, 9, 967012.

INTRODUCING NATURAL DEEP EUTECTIC SOLVENTS IN ARIZONA SOLVENT SYSTEMS FOR SUSTAINABLE USE OF CENTRIFUGAL PARTITION CHROMATOGRAPHY

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Centrifugal partition chromatography (CPC), a support-free liquid–liquid chromatographic technique, can support sustainable separative operations. However, it remains under the reign of organic harmful solvents as tailoring green solvents systems is challenging. Natural Deep Eutectic Solvents (NaDES) represent a new opportunity for a sustainable use of CPC. These ionic solutions encompasses many desirable traits, including their natural origin and their wide range of polarity. NaDES with low viscosity, such as terpene based NaDES, are the most suitable for CPC [1], but their number is limited. In this work, a large screening of based NaDES was carried out to build a collection of potential candidates. Two types of combinations were generated at different molar ratios: “terpene-terpene” and “terpene-organic acid”. Several “terpene-organic acid” NaDES were formed, for which no description in the literature has been provided. Some stable NaDES were discriminated based on their odour and color. One NaDES was selected to be used in CPC. Our strategy is based on introducing the selected NaDES to the ARIZONA family, which is one of the most popular biphasic solvent systems[2].

References: [1] Fan *et al., Global chall.,* 2021, 5(3), 2000103. **[2]** Berthod *et al., Anal. Bioanal. Chem.*. 2005, 383(2), 327-40. **[3]** Faure et al., *Anal. Bioanal. Chem*., 2014, 406, 5909–5917.

Communication 4

ETUDE PHYTOCHIMIQUE ET BIOLOGIQUE DES PLANTES MEDICINALES ANTIMICROBIENNES DE COTE D'IVOIRE POUR UNE VALORISATION THERAPEUTIQUE CONTRE TOXOPLASMA GONDII

OUATTARA Nangouban [1,2,3*], VOUTQUENNE NAZABADIOKO Laurence[1], HUGUENIN Antoine[2], YAO-KOUASSI Philomène Akoua [3], ALABDUL MAGID Abdulmagid [1], ESCOTTE-BINET Sandie [2], VILLENA Isabelle[2].

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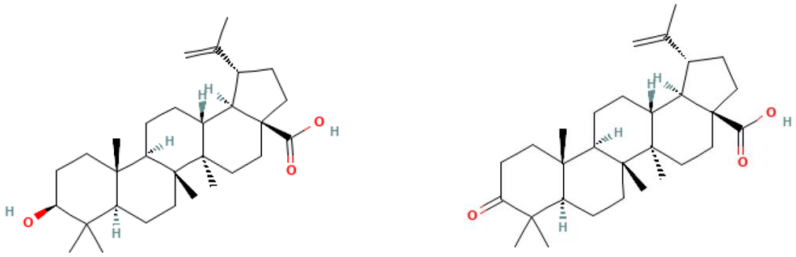
La toxoplasmose est une parasitose ubiquitaire et cosmopolite, due à un protozoaire : *Toxoplasma gondii* (Apicomplexa obligatoire). Asymptomatique et potentiellement dangereuse pour le fœtus, la toxoplasmose nécessite un suivi régulier de la femme enceinte et de son bébé; sa localisation cérébrale est au premier plan chez les patients fortement immunodéprimés (VIH/Sida) **[1]**. Les dernières études épidémiologiques ont montré que la séroprévalence est de 31 % en France et de 45,2% en Côte d'Ivoire **[2,3]**. Le meilleur traitement actuel, est une bithérapie combinant la pyriméthamine et la sulfadiazine, mais ces molécules sont mal tolérées et présentent des chimiorésistances. Devant ce contexte et voulant valoriser des plantes médicinales antimicrobiennes de la Côte d'Ivoire, nous avons entrepris une étude phytochimique bioguidée avec pour objectif de trouver de potentiels métabolites spécialisés bioactifs contre les tachyzoïtes (souche RH, de type I) de *Toxoplasma gondii*.

Une présélection des plantes a été faite par des études bibliographiques (Ethnobotanique, biologique et phytochimique). Neuf espèces ont été récoltées en Côte d'Ivoire donnant 11 drogues différentes que sont : les feuilles de *Combretum micranthum* G. Don (Combretaceae), les feuilles de *Elaeis guineensis* Jacq. (Arecaceae), les parties aérienne de *Erigeron floribundus* Kunth Sch.Bip (Asteraceae), les écorces du tronc de *Oldfieldia africana* Benth. & Hook. f. (Euphorbiaceae), les feuilles et les écorces du tronc de *Octoknema borealis* Hutch. & Dalziel (Olacaceae), les feuilles et les écorces du tronc de *Omphalocarpum ahia* A. Chev. (Sapotaceae), les écorces du tronc de *Omphalocarpum elatum* Miers (Sapotaceae), les parties aériennes de *Tristemma coronatum* Benth. (Melastomataceae) et *Tristemma spp* (Melastomataceae) ont fait l'objet de notre étude.

A l'aide d'une extraction séquentielle de polarité croissante (*n*-heptane, CH_2Cl_2, AcOET, 80% MeOH), nous avons obtenu 44 extraits, qui ont été par la suite criblés contre le parasite à une concentration fixe de 25µg/ml. Dix des 44 extraits bruts se sont avérés non cytotoxiques contre les cellules véro (% viabilité cellulaire ≥ 80%) à 25µg/ml et inhibaient plus de 50% de la croissance parasitaire à 25µg/ml. Deux de ces dix extraits bruts qui présentaient plus de 90% d'inhibition de la croissance parasitaire (l'extrait DCM des écorces du tronc et l'extrait AcOEt des feuilles de *Omphalocarpum ahia*) ont été fractionnés par chromatographie de partage centrifuge puis purifiés par HPLC. Au total**, 41 molécules** dont la grande majorité appartienne à la famille des triterpènes dont **6 nouvelles** ont été décrites. L'indice de sélectivité de 20 de ces molécules non testées sur *T. gondii* dans la littérature **[4,5]** ont été déterminées par chimiosensibilité (0,1-5 µmol/L) ce qui nous a permis de discuter la relation structure-activité quantitative (QSAR) de ces molécules.



Références: **[1]** Richard D. Pearson., Édition professionnelle du Manuel MSD., 2020. **[2]** Robinson E, et al., Eurosurveillance., 2021, 26(5), 1900710. **[3]** Bonouman-Ira et al., Rev int sc méd -RISM., 2017, 5. **[4]** Darme, P et al., Antimicrobial Agents and Chemotherapy., 2022, 66 (1). **[5]** Zhang RH et al., Korean J Parasitol., 2021;59(3):297-301.

ANTIFUNGAL ACTIVITY OF *PETERSIANTHUS MACROCARPUS* (P.BEAUV.) LIBEN TRUNK BARK (LECYTHIDACEAE)

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Petersianthus macrocarpus (P.Beauv.) Liben, Ex. *Combretodendron macrocarpus* (P.Beauv.) Keay (Lecythidaceae) is a tree which occurs in the West and Central Africa rain forests. The trunk bark is used in Gabonese traditional medicine as antalgic, and to treat venereal and fungal infections. So a study was initiated to evaluate the antifungal activity of *P. macrocarpus*.

P. macrocarpus trunk bark was collected in Ngounie province during an ethnobotanical field work. Aqueous extract was obtained by infusion whereas methanol extract was prepared by maceration in methanol. The extracts were tested against seven yeast isolates from vaginal swabs, namely *Candida albicans*, *C. krusei*, *C. tropicalis*, *C. glabrata*, *C. dubliniensis*, *C. famata* and *C. rugosa,* obtained in the medical analysis laboratory of the "Centre Interdisciplinaire de Recherches Médicales de Franceville (CIRMF)". Identification and antifungal susceptibility testing of yeast isolates was performed using Vitek 2 AST-YST cards and Vitek 2 AST-YS08. The antifungal activity was evaluated using the disk diffusion method. The reference antifungal agents were Amphotericin B (10 µg/mL) and Fluconazole (100 µg/mL), and the negative control was DMSO 10%. The Minimum Inhibitory Concentration (MIC) extract was determined using the broth microdilution method containing RPMI 1640.

The methanol extract of *P. macrocarpus* trunk bark (10 mg/mL) was active against five *Candida* species. The most sensitive was *C. krusei* with a diameter zone inhibition of 15 mm, followed by *C. glabrata* (13 mm), *C. albicans*, *C. dubliniensis* and *C. rugosa* (10-12 mm). Amphotericin B exhibited a diameter zone inhibition of 17 mm against *C. krusei* whereas Fluconazole was inactive as described in litterature.

The best MIC was observed with *C. albicans*, *C. dubliniensis, C. rugosa* (0.5 mg/L), followed by *C. krusei* and *C. glabrata* (1 mg/L). None of the *Candida* species tested were inhibited by the aqueous extract.

The obtained results support the ethnomedicinal uses of *P. macrocarpus* in Gabon.

References : [1] Olugbade *et al.* J. Nat. Prod 2000, 63, 716-719 ; **[2]** Tsatsinkou Bomba *et al.* J Ethnopharmacol. 2015, 174, 66-73 ; **[3]** Ferreira *et al.* J. Ethnopharmacol. 2021, 10.1016/jep.2021.114049.

Communication 6

NATURAL PRODUCTS PURIFICATION BY CPC-MS

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In order to reach the high purity required by legislation for Pharmaceutical and Natural Products makes the use of preparive, pilot and industrial scale chromatograpy inescapable for many compound groups. Large scale traditional support media based chromatography uses high volumes of solvent with limited sample loading capacity and a solid media which must be periodicaly replaced.

Centrifugal Partition Chromatography (CPC) is a support-free liquid–liquid chromatography based on the partitioning of solutes between two non-miscible liquid phases (figure 1). The lack of any solid support provides many advantages to CPC over conventional LC, including the ability to inject directly crude extracts into the column to reach a highly pure molecule in one step with low solvent consumption, no need of silica and without irreversible adsorption or compounds denaturation due to silica[1]. This technology is mainly used for the purification of active pharmaceutical ingredients from natural extracts or fermentation slurries[2], for production of analytical standards from complex natural matrices[3] or for academic research to isolate and identify new molecules of interest[4]. When working on drug discovery, combining an online MS detector to directly identify and collect target molecules during a CPC run negates the need for time consuming fraction analysis and reduces the number of fractions collected drastically.

This presentation will details the set up of a CPC-MS system and illustrates its capacity through different example as purification of artemisinin from *Artemisia annua* or piperine from *Piper nigrum*.

Figure 1: From left to right, CPC rotor, disks and cells

References: [1] Pinel et Al *Journal of Chromatography A*, 2007, 1151 : 14–19. **[2]** Audo G et Al. *Gilson application note,* AN-1041**. [3]** Audo G et Al. *Gilson application note,* AN-1036**. [4]** Guido F. Pauli et Al *Journal of Natural Product*, (2008), *71,* 1489–1508. **[5]** Le Quemener et Al. *Gilson application note,* AN-1042

Cette communication, propose par la société GILSON, mécène du symposium, a été soumise à l'approbation du comité scientifique

Communication 7

MULTIBLOCK COMPARISON OF HOP CHEMISTRY AND ITS AROMATIC INFLUENCE AFTER BREWING

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Hop, *Humulus lupulus* L., is a traditional crop of Northern France. Female inflorescences, also named cones or hops, are used in brewing to provide bitterness and aroma to beer, as well as for their antimicrobial properties. These properties are closely connected to their original chemical composition. In particular, hops produce prenylated chalcones including xanthohumol and desmethylxanthohumol and acylphloroglucinol derivatives with humulone analogues (α-acids) and lupulone analogues (β-acids) (Figure 1A). Moreover, hop essential oil is mainly represented by non-oxygenated monoterpenes and sesquiterpenes (*β*-myrcene, *β*-caryophyllene and *α*-humulene) (Figure 1B). The bitterness sought by brewers is due to the α-acids, while the aromas come from the volatile compounds. In recent years, the new interest of consumers for craft and aromatic beers has given a new dynamism to the hop sector in the region. In the continuity of our previous research on the genetic diversity of hops in the region Haut-de-France **[1]**, the present study aims to explore the close link between the chemical composition of hops and the aromatic characteristics of beer. Our study concerns 39 *ex-situ* accessions, i.e. the wild accessions that have been grown in collection in our experimental hop field, which were compared with 10 commercial varieties and 3 heirloom varieties. The phytochemical characterization of hops collected *ex-situ* focused on the quantification of the main prenylated phenolic compounds by UHPLC-UV, non-targeted metabolomic analysis by UHPLC-HRMS, and volatile compound analysis by HS-SPME GC-MS. The beers were brewed with some hops from our collection and were subjected to an organoleptic characterization by a panel of tasters. The different data obtained during these different analyses were correlated by multiblock analysis, revealing a strong distinction between beers brewed with commercial hops and those brewed with wild accessions. In particular, these analyses made it possible to identify chemical markers characteristic of wild hops both terpenoid compounds such as *α*- and *β*-selinene, alloaromadendrene, *β*- and *γ*-elemene, *α*-bergamotene and *β*-acid derivatives.

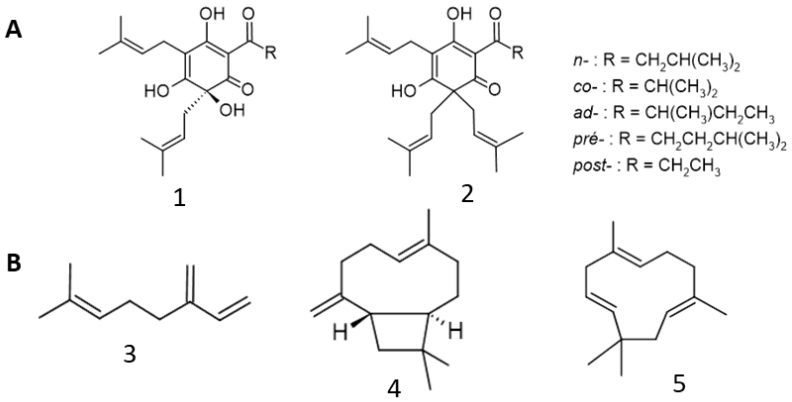

Figure 1: A: chemical structure of α-acids (humulone derivatives) (1) and or β-acids (lupulone derivative) (2). B: chemical structure of the main volatile compounds of hops: *β*-myrcene (3), β-caryophyllene (4) and *α*-humulene (4).

References: [1] Paguet *et al.*, *Phytochem.*, 2023, 205, 113508.

Communication 8

Natural Products Targeting the Unfolded Protein Response (UPR) as a New Biocontrol Strategy

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The Unfolded Protein Response (UPR) is essential for eukaryotes in the control of Endoplasmic Reticulum (ER) protein folding and maturation **[1]**. As far as phytopathogens are concerned, UPR is also an important pathway associated with antifungal resistance. Indeed, UPR depletion in *Alternaria brassicicola* mutants results in a complete loss of virulence as well as a high sensitivity to phytoalexins **[2]**. Therefore, UPR appears as a promising target for the development of new antifungal strategy. In fungi, the UPR signal pathway is only mediated by the transmembrane protein IRE1 **[3]**. Research for inhibitors targeting IRE1 started with the design of an *in vitro* cell-based assay which was then applied to an in-house natural products library. This allowed the identification of seven potential IRE1 inhibitors, highlighting the class of polyhydroxylated prenylated xanthone. Inhibition of *hac*1 mRNA splicing, which is mediated by IRE1, was then validated for the most active compound, namely γ-mangostin. Active xanthones - at subtoxic doses - induced significant reduction in necrosis size for plants inoculated with necrotrophic fungi.

References:

[1] Adams *et al.*, *Front. Mol. Biosci.*, 2019, 6 :11, 1-12.
[2] Joubert *et al.*, *Mol. Microbiol.,* 2011, 79(5), 1305-1324.
[3] Krishnan *et al.*, *Fungal Biol. Rev.,* 2014, 28, 29-35.

Communication 9

PROFILING PLANTS WITH ANTIMALARIAL BLOOD STAGE ACTIVITY USING METABOLOMICS: AN ADDED DIMENSION TO DRUG DISCOVERY

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Natural products and their derivatives have historically contributed significantly to the treatment of malaria. However, despite their promising potency diversity, it is challenging to determine their mode of action (MoA), which is essential for antimalarial drug discovery. Metabolomics is a robust tool that had been successfully used to profile the MoA of antimalarial compounds, but it has seldom been applied to complex matrices such as plant extracts and natural compounds. In this study, three plants were used: Poupartia borbonica Gmel, a dioecious endemic plant from the Mascarene Islands belonging to the Anacardiaceae family, and its alkyl cyclohexenone derivatives with antiplasmodial properties1; Artemisia afra and Artemisia annua, both known for their antimalarial activities2, collected from the Adamawa Region of the Republic of Cameroon in the same season. Trophozoite-synchronized Plasmodium falciparum cultures were treated with extracts and purified compounds derived from these plants and were analysed by LC-MS and 1H NMR metabolomics to estimate their metabolic profile. Results were compared against metabolic responses to established antimalarial drugs with defined MoAs – atovaquone, chloroquine, quinine and artemisinin. Our findings suggest that P. borbonica and isolated compounds are active on hemoglobin metabolism related pathways, whereas A. afra and A. annua have differing profiles, with A. afra affecting nucleotide metabolism and A. annua impacting glutathione metabolism and associated redox pathways. Therefore, metabolomics is a viable tool to profile plant extracts and natural compounds with promising antiplasmodial activity and should be incorporated as a standard screening method in drug discovery.

References: [1] Ledoux, A. *et al.*, *J. Nat. Prod.*, 2017, 80, 1750–1757. **[2]** Maciuk, A., *et al.*, *Nat. Prod. Rep.*, 2023, doi:10.1039/d3np00001j.

Communication 10

Identification of tropical plant immune regulatory molecules inducing Mtb intracellular killing within infected macrophages to shorten TB therapy

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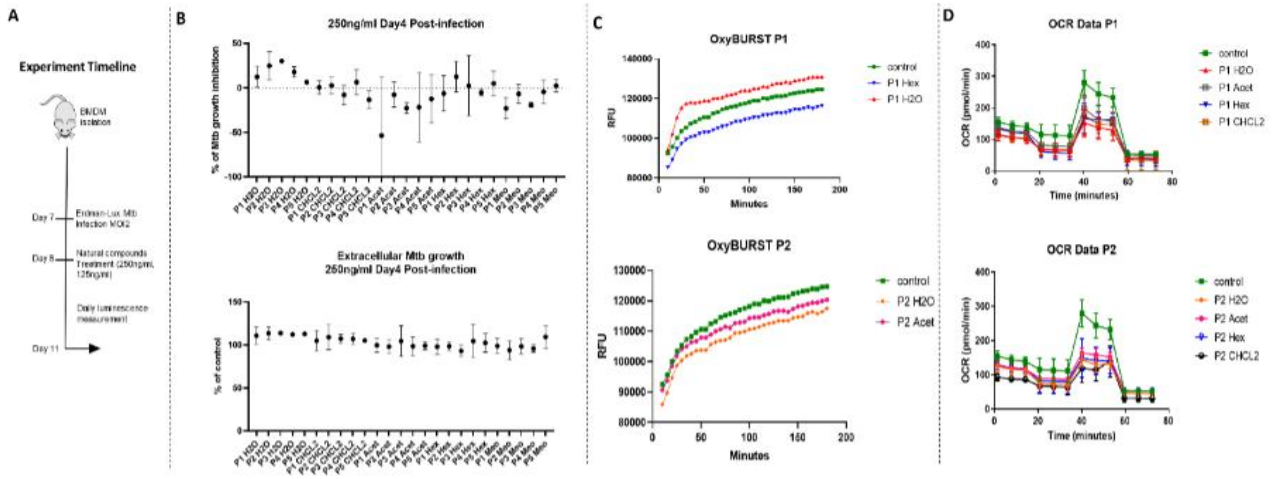
Pulmonary TB is part of the lower tract respiratory diseases together with bronchitis, pneumonia, lung. Pulmonary TB is extremely difficult to treat and required six months antibiotic based therapy. Although this multi-drug therapy is efficient in most TB cases, it failed to completely sterilised lung environment in clinically cured patients leading to recurrent TB disease in many cases within two years of a successful therapy. Furthermore, the current multi-drug therapy is extremely expensive.[1] This situation has significantly favoured the spread of TB disease and the emergence of drug resistant cases. New, shorter and cheaper alternative therapy for TB disease is urgently needed for efficient management of this pandemic. African populations have historically relied on medicinal plants for numerous diseases including respiratory tract infectious diseases like TB[2].

It is in this context that, we selected five plants used in traditional Gabonese medicine to treat lung infections: (*Gossypium barbadense* (Malvaceae); *Pycnanthus angolensis* (Myristicaceae); *Scyphocephalium ochocoa* (Myristicaceae); *Drypetes gossweileril* (Putranjivaceae); *Hallea ledermannii* (Rubiaceae)) based on botanical surveys and the claims from traditional healers about the plantt´ anti TB effects. The extraction was performed in Hexane, Acetate, dichloromethane, methanol and water before evaporation. We performed a serial dilution of each extract from 250 ug/ml to 0.122 ug/ml. Macrophages were infected with Mycobacterium tuberculosis (Mtb) at MOI of 5 for four hours in triplicate and washed. Infected macrophages and Mtb alone were incubated with plant extracts for 48 and 72 hours. The experiment was repeated 3 times.



No plant extract showed a direct effet on extracellular Mtb. We observed 87% and 53% reduction rate of intracellular Mtb with H.ledermannii and Scyphocephalium ochocoa, respectively. The reduction rate was more important in water extracts. *H.ledermannii* and *S. ochoco* could only induce reduction of intracellular Mtb (not Mtb alone) demonstrating their ability to modulate macrophages activation toward killing intracellular bacilli. Further step consists on the islolation of the molecules able to induce phagocytosis, nitric oxide secretion, phagolysosome maturation and reduction of intracellular Mtb from the extracts.

References: [1] WHO, 2019. **[2]** Mounguengui, D et al, Bull. Soc. Pathol. Exot. 105, 1–4 (2012).

Le séneçon en arbre et la renouée du Japon, des plantes invasives à potentiel anti-biofilm et antifongique

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Les champignons levuriformes pathogènes opportunistes du genre *Candida* sont impliqués dans 90% des infections invasives **[1]**. Capables de former des biofilms, ils sont alors résistants à la plupart des médicaments conventionnels.

Dans un contexte de recherche de nouvelles molécules actives contre ces champignons, les extraits de cinq plantes invasives récoltées en France ont été étudiés pour leur potentiel antifongique et anti-biofilm contre *Candida albicans.* Les extraits éthanoliques (100% et 50%) des feuilles de *Reynoutria japonica* ont montré la meilleure activité antifongique avec des CMI_{50} de 250 µg/mL et 15,6 µg/mL respectivement. Concernant l'activité anti-biofilm, l'huile essentielle (HE) obtenue à partir des feuilles de *Baccharis halimifolia* a démontré un effet anti-biofilm significatif contre *C. albicans*, agissant à la fois contre la maturation du biofilm et contre le biofilm déjà formé, âgé de 24h (CI_{50} de 4 et 74 µg/mL respectivement). L'analyse par GC-MS a mis en évidence la présence majoritaire de sesquiterpenes oxygénés (62%) dans cette HE, notamment d'oxyde de β-caryophyllene (37%). Ce composé ainsi que l'oxyde d'aromadendrene-(2) et le (±)-β-pinene, également présents dans l'HE, ont montré des effets significatifs anti-maturation (CI_{50}=9 - 310 µmol/L) et anti-biofilm mature (CI_{50}=38 - 630 µmol/L) de *C. albicans*. De plus, les deux composés : oxyde de β-caryophyllene et oxyde d'aromadendrene-(2) présentent une faible cytotoxicité sur la lignée cellulaire HeLa à la $CI_{50\ biofilm\ mature}$ (<0,7% d'inhibition). Des études ont également été menées contre d'autres espèces de *Candida* opportunistes : *C. glabrata*, *C. krusei* et *C. parapsilosis*, mais *C. albicans* reste l'espèce la plus sensible à cette HE et à ses composés.

Cette étude met ainsi en évidence pour la première fois le potentiel anti-biofilm de *B. halimifolia*, son HE et certains de ses composés (Figure 1).

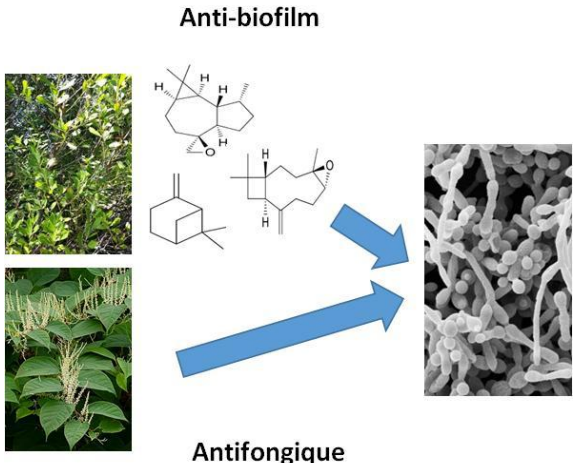

Figure 1: Mise en évidence de l'activité antifongique ou anti-biofilm de *Candida albicans* de *Reynoutria japonica et Baccharis halimifolia*

Référence: [1] Pristov *et al.*, *Clin. Microbiol. Infect.*, 2019, 25(7):792-798.

OSMAC approach applied to mycotoxins production by *Fusarium verticillioides*

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Fungi are capable of producing toxic metabolites, called mycotoxins. In a climate change context, fungal growth conditions are evolving along with the metabolites they produce **[1]**. These environment changes are leading to new mycotoxins production also called "emerging mycotoxins". *Fusarium* can produce fusarial toxins such as trichothecenes, zearalenone, fumonisins **[2]** and "emerging mycotoxins" such as beauvericin, enniatins, moniliformin, fusaproliferin **[3]**. *Fusarium verticillioides* being one of the most important crop pathogens, frequently found in cereals and more specifically in maize, we chose to focus on its ability to produce mycotoxins according to its culture conditions. OSMAC approach has been applied to study culture media and incubation time impact but also to show an overview of *F.verticillioides* mycotoxigenic potential with the adding of epigenetic modifiers in culture medium. On one hand, four epigenetic modifiers, 5-azacytidine (AZA), sodium butyrate (SB), nicotinamide (NIC) and sodium valproate (SV), were used. They alter metabolites production through the induction of silent biosynthetic pathways leading to an enhanced chemical diversity. On the other hand, a kinetic follow-up has been realized to study the fungal growth and mycotoxins production, according to the different culture conditions applied. *F.verticillioides* was inoculated on different media (PDA, MEA, CZA and CMD). A daily follow-up was performed over 21 days. The metabolic profiles obtained from both experiments were analyzed by UHPLC-HRMS/MS under untargeted and targeted metabolomic studies, coupled with a dereplicative approach, allowing to highlight and annotate mycotoxins induced in each culture condition. A modification of the fungal growth but also of the nature and the concentrations of mycotoxins produced was observed according to the modifications of culture conditions and along the time. Indeed, a better understanding of this fungi would allow to understand the conditions of production of fusarial toxins in laboratory and to be able to extrapolate them to products intended for human and animal consumption. The present work emphasizes that *Fusarium verticillioides* has the genetic background to produce a wide diversity of toxigenic compounds.

References: [1] Zingales *et al.*, *Toxins* 14 (7) : 445., 2022. **[2]** Bennett and Klich, *Clin. Microbiol. Rev.* 16 (3) : 497-516, 2003. **[3]** Fraeyman *et al., Toxins* 9 (7) : E228.

Communication 13

DEEP CHEMICAL EXPLORATION OF BALDWIN AND WHITEHEAD BIOSYNTHETIC HYPOTHESIS FOR MANZAMINE ALKALOIDS ENABLED BY DATA SCIENCE

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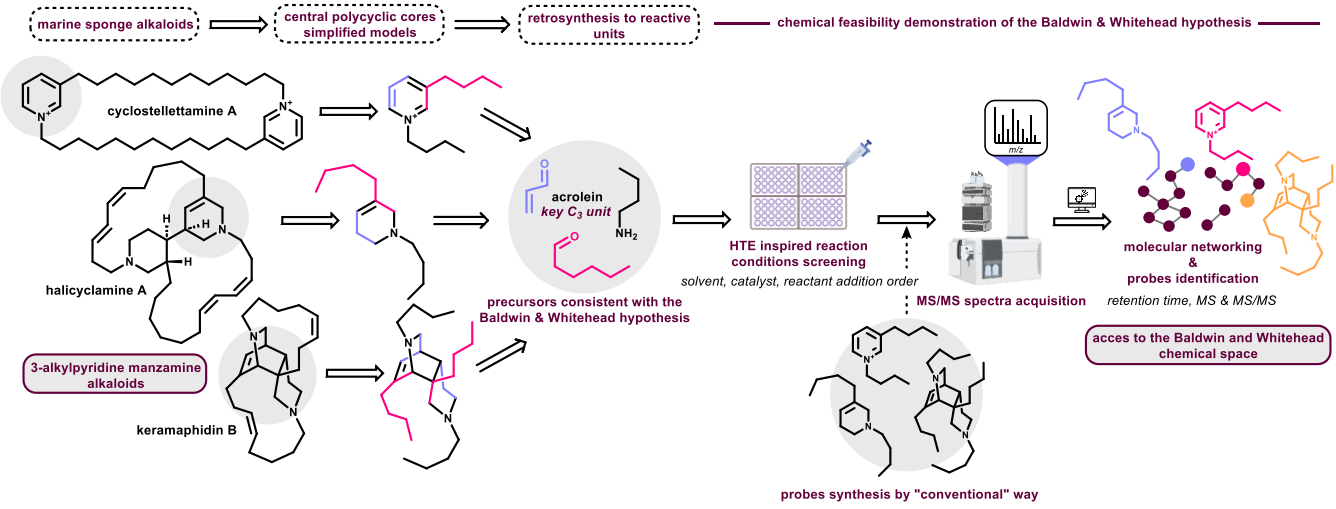
In 1992, Baldwin and Whitehead, in a milestone paper ("On the Biosynthesis of Manzamines")**[1]** disclosed their biosynthetic hypothesis for manzamine A, an emblematic representative of the "manzamine alkaloids" family (including keramaphidin B, halicyclamine A and cyclostellettamines) mainly isolated from Haplosclerida and Dictyoceratida marine sponges.**[2-5]**

To investigate the chemical feasibility of this hypothesis involving aldehydes, primary amines and acrolein (the key C_3 unit put forward by the authors), we have applied an unprecedented set of reaction conditions and synthetic probes-informed molecular networking strategy to decipher information-rich high-throughput experimentations (HTE) of bioinspired multicomponent reactions (MCR).**[6, 7]** From 108 MCR mimicking the biosynthetic proposal leading to manzamine alkaloids, the application of this approach allowed us to access the Baldwin and Whitehead postulated chemical space and answer to a long-lasting hypothesis in the field of marine chemistry.**[8]** Strategy deployed therein is innovative by the use of a complete pipeline involving MCR, HTE and dereplication process applied to the natural products' biosynthesis comprehension.



References:

[1] Baldwin and Whitehead, *Tetrahedron Letters*, 1992, 33, 2059–2062. **[2]** Sakai and Higa, *J. Am. Chem. Soc.*, 1986, 108, 6404–6405. **[3]** Kobayashi *et al.*, *Tetrahedron Letters*, 1994, 35, 4383–4386. **[4]** Jaspars *et al.*, *J. Org. Chem.*, 1994, 59, 3253–3255. **[5]** Fusetani *et al.*, *Tetrahedron Letters*, 1994, 35, 3967–3970. **[6]** Fox Ramos *et al.*, *Nat. Prod. Rep.*, 2019, 36, 960–980. **[7]** Mahjour *et al.*, *Acc. Chem. Res.*, 2021, 54, 2337–2346. **[8]** Leblond *et al.*, *ChemRxiv preprint*, 2022.

Communication 14

L'acide bétulinique, un composé naturel prometteur contre les biofilms inter-règnes

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Le biofilm est un mode de vie répandu chez les microorganismes, y compris chez les microorganismes pathogènes de l'Homme. Actuellement, les médicaments conventionnels sont peu efficaces contre les infections associées aux biofilms. Notre étude vise à rechercher des molécules originales capables d'inhiber les biofilms bi-espèces formés par *Staphylococcus aureus* et *Candida albicans* (*Sa-Ca*). Les plantes invasives représentent un réservoir encore très peu exploré de molécules potentiellement actives. Le postulat de notre étude est que certains de ces métabolites pourraient être des armes pour lutter contre les biofilms, et enrichir notre arsenal thérapeutique.

Quarante extraits issus de cinq plantes aquatiques invasives récoltées en Nouvelle-Aquitaine ont été testés *in-vitro* contre des biofilms bi-espèces *Sa-Ca*. Des extraits de tiges de *Ludwigia grandiflora* se sont montrés les plus actifs avec une inhibition de la biomasse des biofilms matures supérieure à 60 % à 50 µg/mL. (Cristal Violet) Ces extraits actifs ont ensuite été fractionnés, et l'activité anti-biofilm des fractions a été évaluée. Une approche par réseaux moléculaires bioguidés (BBMN) corrélant des données d'analyses par UHPLC-MS/MS des extraits et fractions et les résultats des tests anti-biofilms, a mis en évidence sept composés d'intérêt. L'activité du composé le plus corrélé et le plus abondant, identifié comme l'acide bétulinique, a été caractérisée. Celui-ci réduit de manière significative les biofilms *Sa-Ca* préformés par plusieurs couples de souches de collection et isolats cliniques (inhibition > 40 % à 25 µg/mL) **[1]**. Suite à l'analyse qualitative et quantitative de l'effet de l'acide bétulinique sur des biofilms préformés, par microscopie 3D à fluorescence et cytométrie en flux, nous avons évalué son aptitude à retarder la formation du biofilm. Pour cela, des études mécanistiques ont été menées sur divers facteurs de pathogénicité de *C. albicans* et *S. aureus* : i) propriétés antiadhérentes au cours du développement des biofilms (*Sa-Ca*), ii) son action sur l'hydrophobie de surface cellulaire (*Ca*), iii) sa capacité à perturber la membrane cellulaire (*Ca*), et iv) son influence sur différents facteurs : Quorum Sensing, pompes d'efflux, synthèse de matrices, … via l'étude de l'expression de gènes impliqués dans ces fonctions clés (*Sa-Ca*).

En conclusion, plusieurs composés présumés anti-biofilms ont pu être mis en évidence dans les extraits de *L. grandiflora* grâce à une approche BBMN, parmi lesquels l'acide bétulinique. Ce composé a effectivement montré des perturbations sur différents mécanismes de pathogénicité des cellules formant le biofilm, faisant de lui un futur potentiel candidat médicament contre les biofilms inter-règnes (Figure 1).

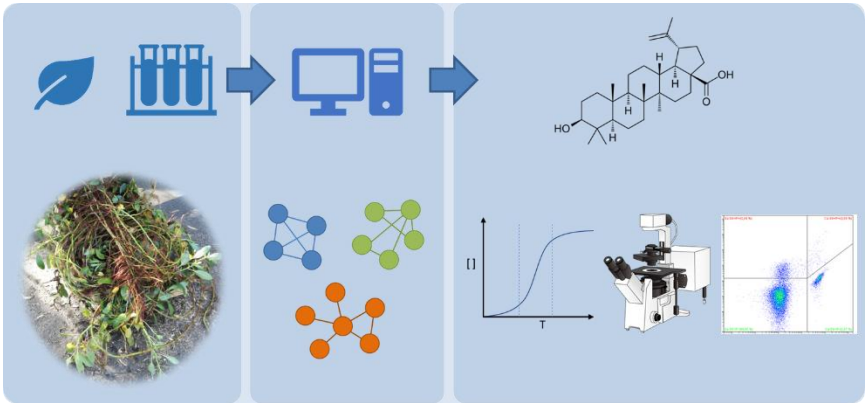

Figure 1 : Identification et caractérisation de l'acide bétulinique à partir des tiges de L. grandiflora

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Isolation of physiological regulators of *Prorocentrum lima* from an associated fungus *Aspergillus pseudoglaucus*.

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Climate change effects in marine waters is a driving factor of increased frequency of harmful algal blooms (HABs) [1]. Understanding the role of biotic interactions is one of the key challenges in HAB ecology, notably in the regulation of microalgal toxin production. In a previous study, we explored chemical interactions between the toxic dinoflagellate *Prorocentrum lima* and a filamentous fungus *Aspergillus pseudoglaucus*, which has been isolated from the microalgal culture itself [2]. Our results highlighted an up-regulation of the dinoflagellate toxins okadaic acid and dinophysistoxin-1 under co-culture condition. Thus, the identification of fungal chemical cues involved in toxins regulation is the next question that we decided to explore.

The fungal crude extract as well as related fractions were evaluated for their effect on *P. lima* physiology, focussing on growth rate and toxin regulations. Fractions showed different effect on extracellular or intracellular concentration of toxins as well as on cell counts. Molecules from active fractions were isolated and further evaluated. For example, cladosporin methyl-ether was highlighted as being able to significantly alter cell count at both low and high concentrations while diketopiperazine derivatives produced an inhibiting effect only at high concentrations. Molecules effect as toxin regulators is still under study.

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Posters : résumés

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Poster 1

Optimization of the extraction of bioactive compounds from the carnivorous plant *Drosera rotundifolia* (round-leaved sundew)

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Drosera rotundifolia (Droseraceae) is an insectivorous plant which is used since mediaeval times as a remedy for coughs and pulmonary diseases [1-3]. The cultivation of this plant by *in vitro* propagation has been developed due to the substantial decline of the *Drosera* habitat. In this study, the extraction of compounds of interest (particularly flavonols) from *D. rotundifolia*, obtained from *in vitro* culture, was optimized using the microwaves and different extraction solvents such as ethanol-water mixtures and NaDES (lactic acid-glucose-water (LGH), propylene glycol (PG)-water). The extraction was carried out using a three-level experimental Box-Behnken design with three factors analyzing the microwave power, the duration of the extraction and the percentage of water.

The comparison of the *D. rotundifolia* extracts' profiles demonstrated that, depending on the extraction conditions used, the detected compounds in the round-leaved sundew extracts may vary quantitatively.

Ellagic acid derivatives (like dimethylellagic acid glycoside) and flavonols (like myricetin, quercetin and kaempferol) as well as their monoglycosyl derivatives were identified in the extracts by comparing their MS and MS/MS data with those of the literature. In addition, the *D. rotundifolia* extracts enriched with specialized metabolites showed interesting antioxidant (DPPH, CUPRAC, iron chelation) and inhibitory activities on enzymes involved in skin aging (especially on elastase). The inhibition percentages for these activities exceeded 60% at 125 µg/ml.

In conclusion, our study aims to the valorization of the carnivorous plant *D. rotundifolia* obtained from *in vitro* culture and offers tools to enrich its extracts in active specialized metabolites.

Keywords

carnivorous plant, *D. rotundifolia*, *in vitro* cultures, specialized metabolites, skin aging protection, green extraction.

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Poster 2

CHROMANNOT – A WEBSERVER FOR REPRODUCIBLE LC-HRMS/MS CHROMATOGRAM ANNOTATION

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One main challenge in the exploration of organisms' chemical diversity remains the annotation of compounds detected within LC-HRMS/MS data, to be able to highlight known and/or unknown metabolites[1]. Having information on all observed/detected peaks from a LC-HRMS/MS chromatogram remains challenging.

At ISOMer laboratory, we developed an entire workflow taking into consideration each step of the general annotation strategy that was particularly adapted for dereplication of specialized metabolites in LC-HRMS/MS profiles. This automated approach based on R (Cran), XCMS[2], IPO[3], CAMERA[4], SIRIUS[5], database search, Taxize [6] and CFMID [7]. Biological origin and MS/MS in silico fragmentation comparison were added into the workflow to improve compound discrimination.

The workflow, which analyses directly raw LC-HRMS/MS data (in open format), was integrated into a web-based interface to ease exploring the annotation result. The ChromAnnot webserver is accessible at https://chromannot.univ-nantes.fr/.

This deep annotation of LC-HRMS/MS data strategy is currently applied to characterize and highlight known/unknown compounds produced various *Penicillium* strains.

This project is funded by the ANR-18-CE43-0013-01 - FREE-NPs project.

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Poster 3

Development of antimicrobial screening of microorganisms associated with a littoral lichen *Rhizocarpon geographicum*

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The phenomenon of antibiotic resistance of various pathogens is a major concern in the scientific community, in different fields of application[1]. The "one health" concept developed in the 2000s include this issue, where the health of humans and plants is interconnected.

Greencell, specialized in the production by fermentation of bacterial and fungal biomasses for agronomy, health and well-being, wishes to develop new ingredients or anti-microbial active ingredients for cosmetics and biocontrol in order to fight against plant pathogens.

The structure/activity relationship of bioactive compounds being established, it is interesting to study atypical ecosystems that are likely to harbor organisms producing compounds with new and/or atypical structures. In this project we are looking at the microorganisms (mainly bacteria) associated with marine or coastal lichens. These littoral lichens, subjected to more drastic environmental conditions than those of their terrestrial counterparts, are thus micro-ecosystems harboring unexplored microbial populations producing uncharacterized and potentially active compounds with various structures[2]. The hypothesis is that these micro-organisms, contributing to the proper functioning of the lichen ecosystem, display different defense mechanisms against potential pathogens. The ISCR has a collection of more than 500 bacterial strains isolated from several coastal samples of *Rhizocarpon geographicum*, subjected to particular abiotic and biotic environmental conditions[3]. The goal of this preliminary work is to develop a streamline process in order to evaluate the antimicrobial activities of our collection strains against 2 plant pathogens, *Erwinia amylovora*[4,5] and *Venturia inaequalis*. In parallel, a more classical assay is also being carried out on two human pathogens *Pseudomonas aeruginosa* and *Staphylococcus aureus* in order to widen the scope of the screened antimicrobial activities and evaluate the selectivity of these activities.

The first step of our screening was to cultivate 380 lichen-associated bacteria in an appropriate medium, to determine their growth curve, to collect the supernatant and pellet at an appropriate phase for the production of specialized metabolites and to evaluate their activities against the targeted plant pathogens.

The first results performed on 40 strains highlighted the inhibitory activities of 3 supernatant samples against *Erwinia amylovora*. One of them exhibited a stronger inhibitory activity than the other two and was chosen for a first fractionation. A process combining various methods of extraction and fractionation led to the attibution of the activity to the most polar fraction. The antimicriobial potential activities of our collection against the other plant pathogen, *Venturia inaequalis* and against *Pseudomonas aeruginosa* and *Staphylococcus aureus* will also be presented.

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Poster 4

Structural prediction and mass-guided isolation of new potentially bioactive compounds from ammoniacum (*Ferula communis* L.)

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The recent proliferation and prevalence of antimicrobial multi-resistant infections has prompted the development of other strategies and alternatives to urgently combat this global threat. For this purpose, past mastering of remedies formulation appears as a wealth of resources for present research. In particular, Arab Medieval Pharmacopeias (AMP) were explored by our interdisciplinary team gathering researchers from biology, chemistry, humanities and informatics sciences **[1]**. One remedy from the Ibn Al-Kindi Pharmacopeia (9th Century) which combines plant-based products and copper was reproduced and biological activity was tested. Ammoniacum, one of the five ingredients, showed antimicrobial activity against gram-positive cutaneous bacteria. This present study aimed to further explore this gum-resin from *Ferula communis* L. using a molecular-networking-guided method for the accelerated discovery of new compounds. HPLC-PDA-HRMS/MS molecular-networking-based dereplication strategy highlighted the presence of known sesquiterpene coumarins (SC) among potential new derivatives by comparison of their MS/MS fragmentation spectra. By this approach, a new hydroxycinnamic-ferulenol (**1**) (Figure 1) derivative was predicted in the extract. Mass-guided isolation followed by structural elucidation allowed us to corroborate the predicted structure of this new SC compound. This targeted isolation led to a total of two known SC (**2, 3**) **[2]** and two new SC structures (**1, 4**). Among those four purified SC, two exhibited antibacterial activity against gram-positive representative bacteria. The results of the present study confirm the interest attached to *Ferula communis* L. gum exploration in the discovery of new structures not described yet with biological properties.

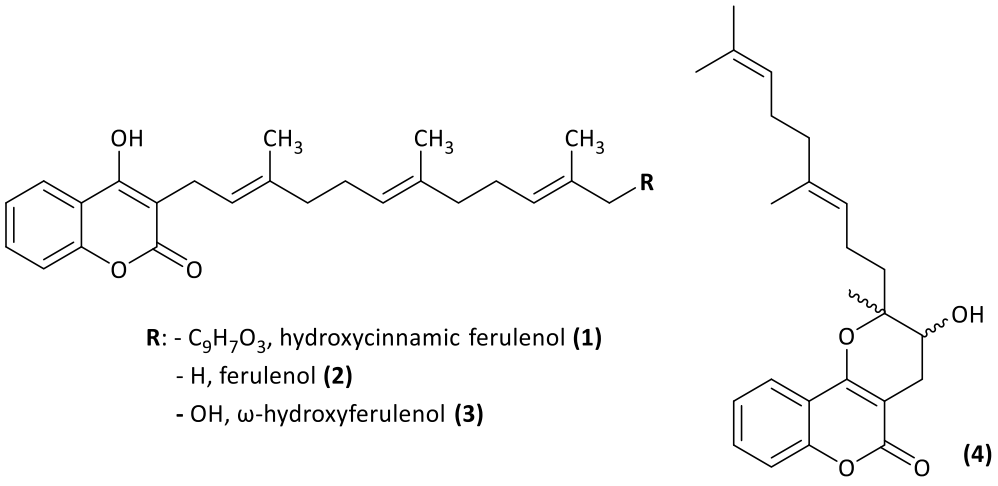

Figure 1: Structure of compound **1-4**

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Poster 5

STRYCHNOS INNOCUA EXPLORATION BASED ON THE COMBINED UHPLC-Q-ORBITRAP-MS/MS METABOLOMICS TOOLS AND SEPARATIVE STUDIES

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Strychnos innocua (Delile) is a plant belonging to the Loganiaceae family, this species with straight-stems reaching 14m high. In Africa, it is used for pharmacological purposes as febrifuges, analgesics and vermifuges **[1]**. The roots are used to manage sickle cell disease **[2]** and treat headaches, cough, meningitis, lumbago, and abscess in association with the leaves **[3]**. Despite the many traditional uses of this plant, few chemical and pharmacological studies have been carried out on the root bark revealing the presence of alkaloids, terpenes, saponins, tannins, flavonoids and steroids **[4]**. So far, only a few common compounds from the plant kingdom have been described, such as umbelliferone, campesterol and β-sitosterol from root bark ethyl acetate extract using a classical technique of extraction, isolation and purification **[5]**.
In recent years, the evolution of analytical methods and treatment tools have made it possible to explore biological sources, since natural products can present a real industrial and pharmaceutical interest.
In this study, the prospection on *S. innocua* secondary metabolites was carried out with UHPLC- MS/MS. The objective of this work is to adapt untargeted metabolomics workflow to this species characterization. Analytical techniques and bioinformatics tools were combined in a high-throughput methodology useful for dereplicating extracts from this plant.
The methanol and hydro-ethanol extracts were analysed by UHPLC-MS/MS, with an ESI-Q/Orbitrap (Exploris 120, Thermo) mass spectrometer. Raw data were pre-processed using the MZMine2 software to get the table of features (figure 1A) **[6]**. Then, MS/MS data were exported to build molecular networks via the Global Natural Products Social Molecular Networking platform **[7]**. The feature-based molecular networking algorithm was employed.

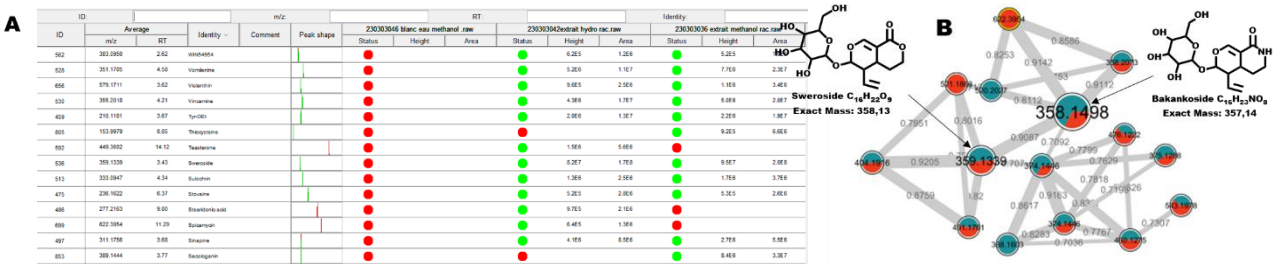

Figure 1: **A)** Example of a feature list from Mzmine with aligned sample blank, hydro-ethanolic and methanolic extracts. **B)** Example of visualisation on cytoscape of GNPS Featured-Based molecular Networking workflow results.

In parallel, a semi-preparative liquid chromatography was used to isolate the predominant secondary metabolites. This methodology allowed us to characterize by 1D and 2D NMR an iridoide the sweroside, and a monoterpene alkaloid the bakankoside, then the main chemical compounds linked to them through the molecular network (figure 1B). In addition, we were able to annotate 132 compounds in both positive and negative mode through databases on a total of 423 features detected; identification of the other compounds is ongoing.

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Poster 6

OPTIMIZATION OF A SUSTAINABLE OIL/WATER EXTRACTION OF ANNATTO (*BIXA ORELLANA* L.)

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Annatto is a red pigment traditionally used for cosmetic, therapeutic and food purposes that is still one of the main natural pigments used worldwide. It is obtained from the seeds of achiote (Bixa Orellana L.), a South American shrub. Plant extracts are a good alternative to mineral or synthetic pigments as they are generally safer and greener. Due to their richness in secondary metabolites, they can also bear multiple activities that can be valorised **[1]**. Achiote is rich in apocarotenoids responsible for the colour. It also contains polyphenols, tocotrienols and tocopherols, with a ratio largely in favour of tocotrienols. those compounds are known for their various activities (antioxidant, photoprotective, anti-aging…) **[2]**. However, they have a wide range of polarity, making it difficult to optimize their simultaneous extraction.

In this study, we suggest a biphasic oil/water extraction assisted by ultrasounds for a cosmetic valorization. This method allows the simultaneous extraction of both polar and non-polar compounds in a pre-formulated extract. Response Surface Methodology was used to optimise the extraction parameters (duration, power and plant to solvent ratio) using the colour of the oil phase and the Total Polyphenol Content of the water phase as responses. Then, different plant oils were compared for their extraction capacity and their impact on colour, activity and stability of the extract using Principal Component Analysis. Both phases of all extracts were also analysed by HPTLC. Reference hydroalcoholic and ethyl acetate extracts were characterised using UHPLC-HRMS to identify the main compounds of the plant sample.

This novel one-step extraction allows the recovery of compounds with a large polarity range in a pre-formulated extract. Its simplicity, potential scalability and efficacy make it interesting for cosmetic valorisation. Moreover, it gives a multipotent ingredient with colour, activity and stability interests.

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Poster 7

HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY (HPTLC) TO PROFILE LICHEN METABOLITES

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Lichens are symbiotic organisms that produce unique secondary metabolites. Phenolic compounds as depsides, depsidones, dibenzofurans… are generally the most abundant and visible compounds. These compounds are of biological and pharmaceutical interest but also of major importance in chemotaxonomically-based identification of some species **[1]**. So standardized protocols have been proposed to characterize them, mainly based on Thin Layer Chromatography (TLC) approaches currently used by lichenologists **[2]**. From these protocols terpenoids are less considered because they are more challenging to visualize and for some phenols free-lichens they can be valuable chemotaxomic markers. Additionally, most of the terpenoids encountered in lichens are hopanoids which is a very special group, only produced in a limited number of living organisms. Like other terpenoids, their physicochemical, biological and pharmaceutical properties merit further study **[3]**.

This work consists in developing standardized analytic methods to profile and identify phenolic compounds and terpene compounds in a simple way. This method is also expected to allow a semi-quantification of the major compounds thanks to calibration curve of standards. HPLC profiling has been used, including hyphenation to a variety of detectors (MS, EDSL, UV) but High Performance Thin Layer Chromatography (HPTLC) is here envisaged with dedicated conditions to visualize phenols and to visualize terpenoids. This technique has been chosen because it allows a rapid (24 samples per plate) and a visual (spots) identification of compounds, overcoming in some case some limitations encountered with HPLC. Moreover, such an approach will facilitate the dialog between lichenochemists and lichenologists, who analyze lichen acetone extracts by TLC.

Therefore, two HPTLC methods have been developed and databases related to phenol and terpene standards were created. Hundreds of standards were used to optimize the migration step and the revelation conditions for each method. For phenolic compounds, a gradient mode (methanol, toluene, dichloromethane) using an AMD2 chamber is proposed, whereas an isocratic mode (chloroform) for terpene was used to separate most of the compounds on a silica plate. A combination of parameters including the spot Rfs, UV (254 nm and 365 nm) absorption, colors before and after derivatization with anisaldehyde sulfuric reagent allowed a first lichen compounds discrimination. For the undifferentiated ones, and particularly for phenolic compounds, full UV spectra, compounds masses (with the scraping tool for MS interface) and in some case a specific KUV (fluorescence at 365 nm after KOH spraying) reaction allowed the final identification. For terpenoids, a semi quantification analysis using an ergosterol calibration curve with phosphomolybdic acid revelation is proposed. Thanks to these databases, combined with a suitable lichen extraction, dozens of complex lichen extracts will be now analyzed in parallel migration. Such an approach is expected to afford an accurate and rapid information about the lichen composition and to facilitate the bioactivity assays through bioautographies.

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Poster 8

ISOLEMENT ET IDENTIFICATION DE NOUVEAUX DITERPENES DE TYPE DAPHNANE : ACTIVATION DE PKCs ET ROLE DANS LE TRAITEMENT DU CANCER COLORECTAL

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La biodiversité végétale représente un réservoir important de molécules originales bioactives. La famille des Euphorbiaceae, en particulier, est connue pour produire un latex contenant de nombreux métabolites secondaires, notamment des diterpènes [1-4]. Ce travail a consisté à étudier le latex de *Hura crepitans* L. (Euphorbiaceae), collecté en forêt Amazonienne, et en particulier les diterpènes de type daphnane qu'il contient en raison de leurs nombreuses activités biologiques [5-7]. Ces métabolites spécialisés sont connus pour être des activateurs de sérine-thréonine kinases PKCs [8-10], des médiateurs enzymatiques particulièrement sous exprimés dans le cancer colorectal (CCR) [11-12]. Malgré la prévention et les thérapies anticancéreuses existantes, le CCR reste le troisième cancer le plus fréquent et le deuxième plus mortel au niveau mondial [13-14], avec un taux de survie à 5 ans de seulement 5 à 15% au stade métastatique [15]. Dans ce contexte, la découverte de nouvelles molécules naturelles activatrices des PKCs pourrait être une piste prometteuse dans la recherche de nouvelles thérapies anticancéreuses.

Le présent travail décrit l'isolement, par différentes méthodes séparatives (colonnes chromatographiques, CLMP, CLHP semi préparative), de sept daphnanes, incluant deux molécules connues (la huratoxine (HT) et la 6'-oxo-huratoxin) et cinq dérivés originaux (les 4'*S*,5'*S*-époxy-huratoxine (EHT), 6'*R*-hydroxy-huratoxine, 4'*S*,5'*S*-dihydroxy-huratoxine, 4'(*Z*)-6'-oxo-huratoxine et la huratoxigénine-20-(11'-méthyloctadéc-12'-énoate)[16]. Les structures de ces molécules ont pu être élucidées grâce à différentes techniques spectroscopiques (UV, HRMS, RMN 1D et 2D, dichroïsme circulaire) et mathématiques à partir de modélisations moléculaires. Les effets des daphnanes isolés ont été évalués sur des cellules humaines de cancer colorectal Caco-2 afin de déterminer des relations structure activité. La HT et l'EHT ont présenté la meilleure activité cytostatique sélective des cellules cancéreuses avec respectivement 20% et 30% d'inhibition de croissance cellulaire à la concentration de 1 µg/mL. Nous avons également montré que cette activité est accompagnée d'un réarrangement cellulaire mimant l'architecture de la crypte intestinale. Des travaux pharmacologiques plus poussés ont permis de montrer l'influence de l'isoenzyme PKCζ sur les activités cytostatiques et morphologiques des deux daphnanes les plus actifs. Enfin, l'activité antiprolifératives de ces composés a été confirmée sur des cellules primaires cancéreuses humaines cultivées sous forme d'organoïdes. La HT et l'EHT inhibent de manière sélective la prolifération des organoïdes cancéreux (40% d'inhibition de croissance) à 0,1 µg/mL. Ces résultats permettent donc d'envisager d'évaluer ses composés sur des modèles murins de cancer colorectal.

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DEREPLICATION OF NORLICHEXANTHONES IN LICHEN EXTRACTS: LC/MS VS NMR

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Xanthones are secondary metabolites derivating from the 9*H*-xanthen-9-one scaffold produced by a wide range of plant, bacterial and fungal species **[1]**. In lichens, they occur mostly as members of two families: lichexanthones and norlichexanthones, differing by the methylation of positions 3 and 5 for lichexanthones **[2]**. Positions 2, 4, 5 and 7 may be chlorinated, resulting in a total of sixteen different norlichexanthones for only five different exact masses. This high number of isomers makes them tedious to identify; high resolution tandem mass spectrometry is of no help without HLPC separation combined to standard compounds availability, and even NMR on pure compounds could be tricky, due to their high proton-deficiency.

However, they are of chemotaxonomic interest for lichenologists to identify crustaceous lichens with very similar morphology, such as some species of *Lecanora*.

We therefore constituted a library of the sixteen norlichexanthones, which were obtained by a combined strategy of synthesis and isolation. An HPLC/MS method was set up to separate them efficiently by their m/z and retention times (Figure 1A). In parallel, we acquired NMR data to perform the dereplication of these compounds in lichen extracts, based on the HSQC correlations observed for the non-chlorinated positions (Figure 1B).

While LC/MS is sensitive and easy to interpret, NMR is robust and highly reproducible. A combination of both methods provides a good overview of the xanthone content in lichens.

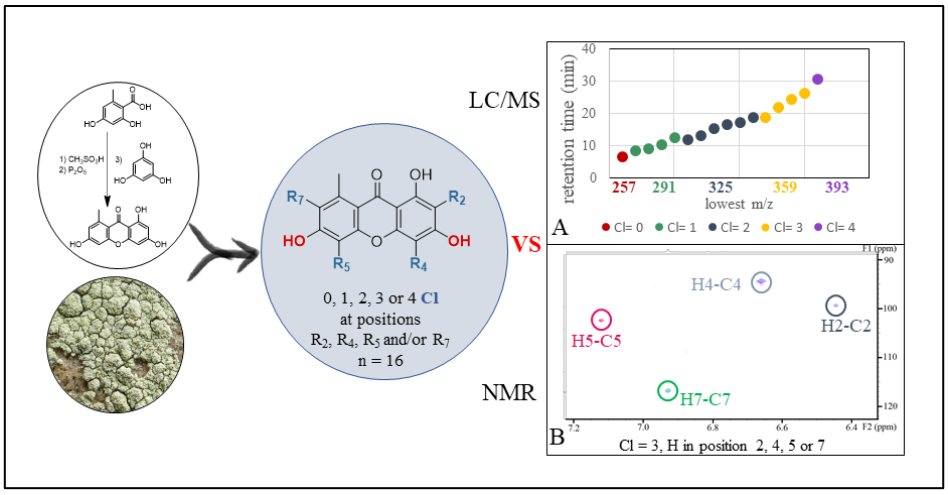

Figure 1: Norlichexanthones in lichens: two complementary dereplication strategies

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Poster 10

CHEMICAL INVESTIGATION OF THE HALOTOLERANT YEAST *HORTAEA WERNECKII*

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Hortaea werneckii (Ascomycota) is a halotolerant black yeast, distributed primarily in hypersaline, marine and in terrestrial environments, from Atacama Desert rocks to deep sea water **[1,2]**. So far, this species was mainly studied as a biological model to understand the halotolerance mechanisms in eukaryotic cells **[3,4]**. While some biosynthetic gene clusters seem to be present in this yeast **[5,6]**, very few chemical investigations have been carried out, making *H. werneckii* an interesting candidate for the discovery of new metabolites and bioactive molecules.

The aim of this study was to investigate the chemical diversity of 64 different strains of *H. werneckii*, both haploid and diploid, isolated from multiple environments and grown on two different culture media (MEA with and without salt) **[1]**. Therefore, a metabolomic study was conducted in order to compare their composition and highlight some interesting chemical entities. So far, a total of 398 lyophilized samples (3 replicates per sample) were extracted with ethyl acetate and one replicate of each sample was analysed through UHPLC-HRMS/MS. The data were treated with MZmine software and subjected to MetaboAnalyst.

A strain isolated from Atlantic hydrothermal springs (*Hortaea werneckii* UBOCC-A-208029) was further subjected to a comprehensive study, in order to isolate and identify antimicrobial compounds. The ethyl acetate extract of this strain showed a promising activity against MRSA (IC_{50} value 16.2 ± 0.3 µg/mL). Fractionation was conducted by Flash chromatography and semi-preparative HPLC. Characterization of the purified compounds will be performed based on NMR and HRMS data, and their activity against MRSA will be evaluated.

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Poster 11

INFECTIONS INVOLVING *CANDIDA ALBICANS* BIOFILMS: IS THE SOLUTION IN LICHENS?

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Evernia prunastri is a common epiphyte lichen growing in abundance in France. The LICSYFILM project (ANR JCJC 2017-2022) studied the effects on *Candida albicans* biofilm of its main metabolites, their synthetic derivatives and also its associated fungi. Association of phytochemistry, medicinal chemistry, microbial biology and metabolomic approaches led to the characterization of several compounds of interest, active against *Candida albicans* biofilm.

Thus, anti-maturation and anti-biofilm assays were performed in microplates by treating 2h- or 24h-old biofilms of *C. albicans* (ATCC 28367 or clinical strains) for 24h or 48h. The residual biofilm after-treatment was quantified using XTT assay. Evernic acid, a depside produced in large quantity by *E. prunastri* inhibited preformed *Candida albicans* biofilm at 50 µg/mL without antifungal activity [1]. Despite this interesting activity, this natural compound has a high toxicity on HeLa and MRC5 cells ($50 < IC_{50} < 60$ µg/mL) leading to the research of closely related compounds. Thus, the extraction and isolation of 6 related depsides and the design and synthesis of 16 derivatives was conducted in order to establish structure-activity relationships. The synthetic depside D8 shows an interesting activity against mature biofilm ($12.5 < IC_{50} < 25$ µM), which has been confirmed in an *in vivo* model of infected catheters [2]. In parallel, fourteen strains of endolichenic fungi (EF) were grown on three culture media and extracted with ethyl acetate. Anti-maturation and anti-biofilm assays as previously described were performed with the thirty-eight extracts obtained. All extracts were also analyzed by HPLC-ESI(–)HRMS/MS to investigate their chemical composition in relation with their antibiofilm activity [3]. After a treatment of 48h at 100 µg/mL, ten extracts reduced significantly ($p \leq 0.0002$) the maturation of the biofilm by at least 50%. Among them, four extracts were also able to inhibit significantly ($p < 0.0001$) a preformed biofilm after a 48h treatment, using both the reference strain and clinical isolates of *C. albicans* [4]. *Preussia persica* extract was the most active, inducing a non-strain-dependent activity against preformed biofilm (inhibition of at least 57%). Molecular networks highlighted interesting and biologically active molecular groups like oxygenated fatty acids and cyclopeptides. The MS-targeted isolation performed on *P. persica* extract allowed the identification of a new highly oxygenated fatty acid. The poor number of annotated compounds showed the importance of phytochemical studies on EF to enlarge fungal chemical databases. In this project, regarding the different investigations carried out, the potential of oxygenated fatty acids and depsides in *Candida* biofilm destruction was highlighted, paving the way for promising perspectives [5].

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Poster 12

OSMAC approach applied to mycotoxins production by *Fusarium verticillioides*

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Fungi are capable of producing toxic metabolites, called mycotoxins. In a climate change context, fungal growth conditions are evolving along with the metabolites they produce **[1]**. These environment changes are leading to new mycotoxins production also called "emerging mycotoxins". *Fusarium* can produce fusarial toxins such as trichothecenes, zearalenone, fumonisins **[2]** and "emerging mycotoxins" such as beauvericin, enniatins, moniliformin, fusaproliferin **[3]**. *Fusarium verticillioides* being one of the most important crop pathogens, frequently found in cereals and more specifically in maize, we chose to focus on its ability to produce mycotoxins according to its culture conditions. OSMAC approach has been applied to study culture media and incubation time impact but also to show an overview of *F.verticillioides* mycotoxigenic potential with the adding of epigenetic modifiers in culture medium. On one hand, four epigenetic modifiers, 5-azacytidine (AZA), sodium butyrate (SB), nicotinamide (NIC) and sodium valproate (SV), were used. They alter metabolites production through the induction of silent biosynthetic pathways leading to an enhanced chemical diversity. On the other hand, a kinetic follow-up has been realized to study the fungal growth and mycotoxins production, according to the different culture conditions applied. *F.verticillioides* was inoculated on different media (PDA, MEA, CZA and CMD). A daily follow-up was performed over 21 days. The metabolic profiles obtained from both experiments were analyzed by UHPLC-HRMS/MS under untargeted and targeted metabolomic studies, coupled with a dereplicative approach, allowing to highlight and annotate mycotoxins induced in each culture condition. A modification of the fungal growth but also of the nature and the concentrations of mycotoxins produced was observed according to the modifications of culture conditions and along the time. Indeed, a better understanding of this fungi would allow to understand the conditions of production of fusarial toxins in laboratory and to be able to extrapolate them to products intended for human and animal consumption. The present work emphasizes that *Fusarium verticillioides* has the genetic background to produce a wide diversity of toxigenic compounds.

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Poster 13

LE JEU D'EVASION : UNE ACTIVITE PEDAGOGIQUE INNOVANTE POUR EVALUER LES CONNAISSANCES EN PHYTOTHERAPIE DES FUTURS PHARMACIENS D'OFFICINE

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Contexte : L'enseignement des sciences pharmaceutiques reste assez traditionnel et scolaire alors que les étudiants sont de plus en plus en demande de pratiques pédagogiques innovantes et stimulantes en relation plus étroite avec la pratique professionnelle **[1,2,3]**. Des centres de simulations médico-pharmaceutiques sont créés dans facultés de médecine et de pharmacie. La présente communication décrit la méthodologie de construction d'un jeu d'évasion au sein des pharmacies expérimentales des facultés de pharmacie de Limoges et de Bordeaux. **But :** Ce travail propose une méthode de validation des connaissances acquises en phytothérapie par les étudiants en 2ème cycle des études pharmaceutiques filière officine en immergeant les apprenants dans leur futur environnement professionnel (pharmacie) et en s'appuyant sur la manipulation concrète de produits présents sur les rayonnages. **Méthodes :** un groupe de travail constitué d'étudiants en pharmacie, d'enseignants chercheurs en phytochimie et en pharmacie galénique, et d'un professionnel du jeu d'évasion a été constitué. Puis des réunions de brainstorming ont permis d'associer chaque objectif pédagogique à une énigme présentée de façon ludique. Après articulation des différentes énigmes entre elles et au sein d'un scénario général, les réflexions ont conduit à la rédaction d'une scénarisation détaillée. **Résultats :** un parcours au sein de la pharmacie expérimentale a été construit autour de 8 objectifs pédagogiques. L'ensemble des énigmes peuvent être résolues en 60 minutes par une équipe de 5 à 7 joueurs. **Conclusion :** le jeu d'évasion élaboré permet aux étudiants de mobiliser des connaissances acquises pour résoudre une situation problème au travers de la fouille d'objet, la manipulation de produits à base de plantes et la réflexion. Il permet de développer plusieurs points clés de leur futur métier (coopération et communication au sein d'une équipe, rapidité et pertinence des choix effectués) tout en apportant un aspect challenge apporté par le chronomètre et la comparaison avec les autres équipes.

Références : [1] Jensen, Teaching with the Brain in Mind, 2nd ed., 2005. **[2]** Sera *et al.*, *Curr. Pharm. Teach. Learn.*, 2017, 9, 155-159. **[3]** Ng *et al.*, *Curr. Pharm. Teach. Learn.*, 2021, 13, 479-491.

Poster 14

MISE EN PLACE D'UNE INTERACTION ENTRE ETUDIANTS DE DEUX FACULTES LORS DE TRAVAUX DIRIGES INTERACTIFS EN PHYTOTHERAPIE

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Contexte : L'enseignement des sciences pharmaceutiques reste assez traditionnel et scolaire alors que les étudiants sont de plus en plus en demande de pratiques pédagogiques innovantes et stimulantes en relation plus étroite avec la pratique professionnelle **[1]**. Ces dernières années, de nombreuses initiatives d'innovation pédagogique voient le jour dans différentes disciplines, visant à impliquer et stimuler davantage les étudiants dans leurs apprentissages **[2,3]**. **But :** La présente communication décrit la mise en place d'un enseignement dirigé en phytothérapie impliquant une communication entre les étudiants de la faculté de pharmacie de Limoges avec ceux de Bordeaux. Une série d'exercices est ainsi proposée impliquant soit une coopération entre les étudiants d'origine facultaire différente soit une compétition entre les deux universités. **Méthodes :** La construction des exercices pédagogiques a été réalisée en utilisant différents outils informatiques. Le logiciel Storyline a été utilisé pour la création de deux cas de comptoir phyto-pharmaceutiques. Wooclap a été utilisé pour un test de connaissances comparatif. Enfin, le module de visioconférence Zoom Meeting associé au logiciel VoiceMeeter Banana ainsi que des micro-casques et des caméras ont permis aux étudiants de communiquer entre eux. **Résultats :** Un enseignement dirigé d'une durée de 2 h a été mis en place en DFASP1 filière officine pour l'Université de Bordeaux (environ 80 étudiants) et en DFASP2 filière officine pour l'Université de Limoges (environ 40 étudiants). Cet enseignement dirigé comprend 5 exercices différents dont 2 en coopération entre sites distants (groupes de 3-5 étudiants), 2 en compétition et 1 exercice individuel. Les échanges entre étudiants sont nombreux et l'implication et la motivation des étudiants est réelle. **Conclusion :** Cet enseignement dirigé prenant la forme d'exercices ludiques et interactifs stimule et contribue à l'apprentissage des étudiants en phytothérapie par le partage d'expériences et le ressenti d'émotions positives. Il pourra servir de modèle pour le développement d'enseignements innovants dans d'autres disciplines difficiles à appréhender par les étudiants.

Mots clés : phytothérapie, sites distants, interactions, compétition, innovation

Références : [1] Jensen, Teaching with the Brain in Mind, 2nd ed., 2005. **[2]** Sera *et al.*, *Curr. Pharm. Teach. Learn.*, 2017, 9, 155-159. **[3]** Ng *et al.*, *Curr. Pharm. Teach. Learn.*, 2021, 13, 479-491.

New oleanane-type saponins from the aerial parts of *Gundelia tournefortii*

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Gundelia tournefortii L., first discovered in the Aleppo region of Syria, is an edible plant that has generated significant interest as a medicinal plant [1]. It has been extensively consumed in traditional medicine in the Levant (Near East) for the treatment of diabetes **[1, 2]**. Saponins are triterpenoid glycosides known for their vast panel of biological properties, among which is their hypoglycemic activity **[3]**. The phytochemical study of *G. tournefortii*, collected from the mountains of Northern Lebanon, led to the isolation of six oleanane-type glycosides from an aqueous-ethanolic extract of the aerial parts. After successive purifications by various chromatographic methods**,** such as vacuum liquid chromatography (VLC), medium pressure liquid chromatography (MPLC), on normal and reverse phase (RP-18 silica gel), and size exclusion chromatography on Sephadex LH-20, their structures were elucidated by an extensive 600 MHz NMR analysis including 1D and 2D NMR experiments as well as ESI-MS. Among the six isolated saponins (**1**-**6**), five have never been reported before (**1**-**5**): 3-*O*-α-L-arabinopyranosyl-(1→2)-β-D-glucuronopyranosyl-3β,29-dihydroxyolean-12-en-28-oic acid 28-*O*-β-D-glucopyranosyl ester (**1**), 3-*O*-α-L-arabinopyranosyl-(1→2)-β-D-glucuronopyranosyl-3β,29-dihydroxyolean-12-en-28-oic acid (**2**), 3-*O*-α-L-arabinopyranosyl-(1→2)-β-D-glucuronopyranosyl-3β-hydroxyolean-12-en-28,29-dioic acid (**3**), 3-*O*-β-D-glucopyranosyl-(1→4)-β-D-glucuronopyranosyl-3β,29-dihydroxyolean-12-en-28-oic acid (**4**), 3-*O*-β-D-glucopyranosyl-(1→4)-β-D-glucuronopyranosyl-3β,29-dihydroxyolean-12-en-28-oic acid 28-*O*-β-D-glucopyranosyl ester (**5**), and 3-*O*-β-D-glucopyranosyl-(1→4)-[β-D-glucopyranosyl-(1→2)]-β-D-glucuronopyranosyl-oleanolic acid (**6**). The stimulation of the sweet taste receptor hTAS1R2/TAS1R3 by *G. tournefortii* saponins was evaluated based on the similarity of their structures with glycyrrhizin from licorice **[4]**.

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Poster 16

TREE SPECIES FROM FRENCH GUIANA: DEREPLICATIVE ANALYSIS AND ANTICIPATION OF NATURAL PRODUCTS

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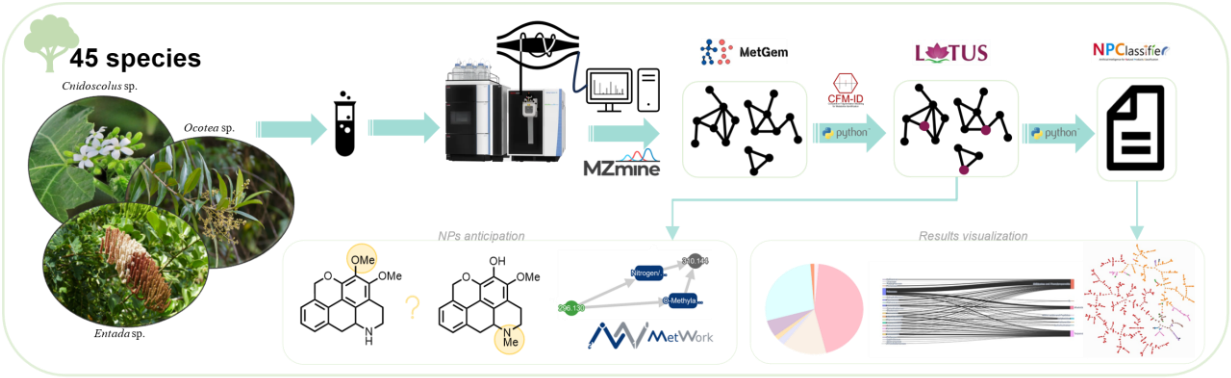
French Guiana is an overseas department and region that abounds in extraordinary biodiversity: 97% of its territory is covered by various types of vegetation and represents a part of the Amazon rainforest.**[1]**

Samples of 45 species (43 genera and 26 families) of trees were collected to explore the molecular diversity of their extracts. High-resolution mass spectrometry analysis was conducted to obtain a suitable dataset for dereplication analysis. To perform the annotation process, an in-house *in silico* library was generated from Lotus database.**[2]** Natural substances identified in our samples showcase a wide range of molecular diversity that we were able to highlight using a structural-based classification tool, NPClassifier.**[3]**

In literature, studied species account for 57.3% of terpenic compounds, whereas our annotations only represent 27.9% of them. Most of the identified compounds are flavonoids (44.6%). Flavonoids are predominant in species of the Fabaceae family (most represented in our datasets with 6 species). Our global molecular network comprises 6431 ions, but only 5.6% of the compounds could be annotated using a library from our taxonomic families. The annotated alkaloids mainly belong to the aporphine class, which forms the largest cluster in the Annonaceae family. In order to have an efficient data processing, analysis and visualization (TMAP and Sankey diagram) of the entire dataset, efforts were made to leverage Python programming.

In addition, MetWork, an *in silico* metabolization tool was used to anticipate new potential metabolites.**[4]** With aim of doing an annotation selection between them we attempt to develop a workflow based on the Bayes theorem and the Tanimoto score.**[5, 6]**

In essence, this work is an exploration of trees' metabolome data using computational chemistry and it allowed us to discover both possible new molecules and to assign previously identified molecules from related species to our specific Guianese trees.



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Poster 17

ANTILEISHMANIAL ACTIVITY OF EUGENOL: TOWARDS ELUCIDATING ITS MECHANISMS OF ACTION

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Leishmania, a neglected tropical disease, remains a health risk in several parts of the world with thousands of new cases of per year **[1]**. Reports of relapse or resistance to current treatments fuel the search for other promising molecules as lone therapy or in combinational treatments **[2]**.

Eugenol (a phenylpropanoid) has shown *in vitro* antileishmanial activity against *Leishmania mexicana mexicana* (*Lmm*) promastigotes with an IC_{50} of 2.72 µg/mL and a high selectivity index **[3]**. Nonetheless, its mechanisms of action have yet to be studied. We here evaluated its effect using a large range of concentrations on the fluidity of *Lmm* membranes by 1,6-diphenyl-1,3,5-hexatriene (DPH) anisotropy, on the metabolic activity with the Alamar Blue assay and lipid droplet abundance by fluorescence microscopy using Nile Red labelling. At concentrations below 10× IC_{50}, a decrease in metabolic activity associated with the maintenance of membrane integrity was revealed. Moreover, a dose-dependent decrease of lipid droplets was observed for concentrations ranging between 0.5 and 5× IC_{50}. These effects observed at low concentrations differ from those observed at higher concentrations (≥ 22.5× IC_{50}), such as an increase in membrane fluidity by 20–30%. We hereby demonstrate that the antileishmanial activity of eugenol does not directly involve alterations in plasma membrane properties, but rather target the lipid storage of *Lmm*.

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Poster 18

Exploring toxin diversity and distribution in french species of *Amanita* from the section *Phalloideae*

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As one of the most iconic mushrooms, *Amanita phalloides* (Fr.) Link, also known as the death cap, holds the reputation of being the deadliest fungi in the world, probably due to its widespread repartition throughout the globe. However, five species of the so-called *Phalloideae* section are known to occur in France since one can also find the famous *Amanita virosa* Bertill. (or destroying angel), the invasive *Amanita amerivirosa* Tulloss., L.V. Kudzma & M. Tulloss., *Amanita verna* Bull. ex Lam. and the newly described *Amanita vidua* Gasch, G. Moreno & P.-A. Moreau[1]. Three classes of toxins can be found within those mushrooms, amatoxins, phallotoxins and virotoxins. Only amatoxins, as inhibitors of DNA polymerase II, are presumed to step in their toxicity by liver and kidney failure. Despite global public awareness of the deadly risk associated with those mushrooms, *Amanita* species are still responsible nowadays for numerous people's death all over the world. Nevertheless, the current knowledge on the chemical content of these *Amanita* species mostly relies on traditional analytical approaches (*i.e.* TLC or HPLC-DAD-MS)[2] and did not yet benefit from the landmark advances in analytical chemistry. To get a better insight into the toxin content of french lethal *Amanita* species, a molecular networking-based workflow was leveraged, benefitting from a taxonomically informed annotation using timaR[3] and further enhanced with DEREPLICATOR-based *in silico* annotations[4]. The restricted distribution disclosed by some further chemical features in the obtained molecular network could be of chemotaxonomic interest.

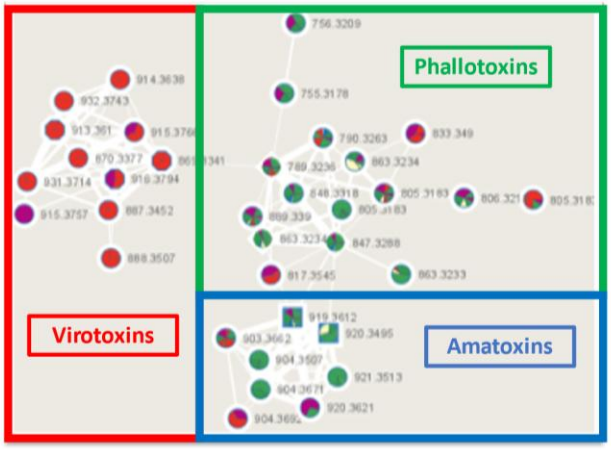

Figure 1: Cluster of *Amanita* toxins in french species from the section *Phalloideae* molecular network.

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Poster 19

Phytochemical investigation of *Salvia officinalis* and *Centella asiatica*

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Salvia officinalis and *Centella asiatica* belonging to the Lamiaceae and Apiaceae families, respectively, have been identified as potential sources of antiallergic compounds due to their rich polyphenolic composition. Allergic diseases are a significant global health concern, with the World Health Organization projecting that at least 50% of the world's population will experience an allergic disease by 2050. **[1, 2]**

This preliminary study aims to characterize of the compounds that are present in the ethanolic extracts of these two plants, with the goal of identifying potential antiallergic compounds. Both *S. officinalis* and *C. asiatica* exhibited a high polyphenolic content, a characteristic known within their respective families and potentially associated with antiallergic properties. This preliminary study highlights the potential of these two plants as valuable sources for the discovery of future antiallergic compounds.

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Poster 20

TARGETED EXPLORATION OF BIO-INSPIRED CASCADE REACTIONS: A ONE-POT TOTAL SYNTHESIS OF NESTERETAL A

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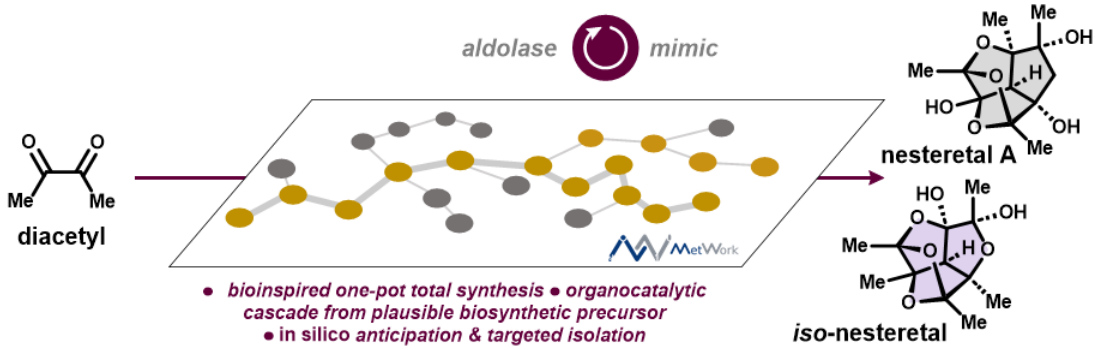
Nesteretal A, a representative of a novel class of cage-like metabolites, was isolated in 2019 by Yang *et al*. from the coral-derived actinomycete *Nesterenkonia halobia*.**[1]** This new molecule exhibits an intriguing complex structure with four intricated cycles, six quaternary carbons and three tertiary alcohols. The biosynthetic pathway proposed by the authors involving diacetyl as a plausible and unique precursor makes nesteretal A an interesting and challenging synthetic target for a bio-inspired total synthesis.

From diacetyl, by a succession of self-aldolizations/hemiacetalizations catalyzed by (*S*)-proline mimicking an aldolase we realized an expeditious one-pot total synthesis of nesteretal A.**[2]** Versatility in the diacetyl auto-assembly prompted us to explore the "bioinspired metabolomes" created in the flask using chemoinformatic tools such as MetWork.**[3]** This powerful *in-silico* anticipation tool allowed us to illuminate the hypothetic biosynthetic pathway leading to nesteretal A, along with a wide chemical space including nesteretal A-like cage molecules. Among them, *iso*-nesteretal which was anticipated, targeted, and isolated.

This work falls within the scope of a trend where chemoinformatic and natural products chemistry are becoming closely linked**[4, 5]** with an innovative and concrete application in total synthesis.



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Poster 21

HALOGENATION OF ETHANOL EXTRACT FROM *PAEONIA SUFFRUTICOSA*: EXPLORING PROMISING PATHWAYS FOR ANTI-SARS-COV-2 MEDICATION DEVELOPMENT

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The COVID-19 pandemic is now considered as an established and ongoing health issue according to the World Health Organization, presenting challenges worldwide despite available pharmaceutical interventions. In response to the pandemic, the Chinese government has proposed the use of Traditional Chinese Medicine (TCM) as a complementary approach to conventional treatments. TCM, deeply rooted in Asian healthcare, has gathered interest for its potential application in Western countries.

The present study focuses on preliminary investigations of halogenation processes applied to the ethanol extract obtained from Paeonia suffruticosa, a traditional Chinese plant, with the aim of enhancing its biological activity, particularly against SARS-CoV-2. Before achieving hemisynthesis on the crude extract, quercetin was choosen to find the optimal reaction conditions of the halogenation step, considering its presence in Paeonia suffruticosa, its abundance and cost-effectiveness. Various halogenation methods were evaluated, including the use of N-bromosuccinimide and an environmentally friendly (green) approach using sodium bromide and hydrogen peroxide. Both methods yielded promising results after LC-MS monitoring.

The green methodology was then used on the Paeonia suffruticosa ethanol extract, successfully generating brominated derivatives, such as dibromopaeonol and dibromooxypaeoniflorin. In conclusion, this preliminary study highlights the potential of halogenation processes to modify the ethanol extract from Paeonia suffruticosa and potentially enhance its anti-SARS-CoV-2 properties. These findings provide insights into the potential interest of TCM in the development of new lead compounds to fight the ongoing global COVID-19 pandemic.

Further investigations are however needed to validate these results and explore other promising late-stage functionalization strategies, using innovative green synthetic approaches.

Poster 22

Chemical interactions between fungal endophytes isolated from *Bixa orellana* L. (Bixaceae)

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Fungal endophytes chemical study has increased this last decade, since many secondary metabolites have been isolated from this hidden source [1]. As they live within a real ecosystem, constantly interacting either with their host-plant and its microbiome, they may represent a source of bioactive metabolites. An equilibrium between the partners of this ecosystem is established through chemical communication, including the biosynthesis of specialized metabolites.
An endophytic strain of *Cophinforma mamane* isolated from *Bixa orellana* L. (Peru) leaves has been studied in our lab for its production of secondary metabolites, especially the thiodiketopiperazines botryosulfuranols A-C [2]. As conventional cultures in laboratory limit the huge potential of novelty of these microorganisms, different methods including epigenetics, “One-Strain Many Compounds” approach and co-cultures have been carried out to modulate its metabolome with two goals: to search for new compounds and to increase the production of botryosulfuranols [3-5]. Here, *C. mamane* was co-cultured with nine endophytic fungal strains also isolated from *B. orellana* and belonging to different genera. As they live naturally in the same ecological habitat, they will likely compete for similar nutrient resources, resulting to interactions that may activate biosynthetic gene clusters encoding for metabolites to overcome those interactions. Phenotypic study showed interaction zones, including pigmentation and inhibition zones in four co-cultures. Extracts of axenic strains and co-cultures were analyzed by LC-HRMS/MS. Comparison of metabolomic profiles and statistical analyses using MZMine and MetaboAnalyst highlighted an increased production of botryosulfuranol A especially when *C. mamane* was co-cultivated with a *Nigrospora* sp. strain. Moreover, new compounds unique to co-cultures could be detected and may correspond to molecules involved in fungal communication. Interaction zones will be soon specifically and chemically characterized.

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Poster 23

NEW METHODOLOGY FOR THE ROUTINE AUTHENTICATION OF RAW MATERIALS ADAPTED TO HERBAL PRODUCTS.

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Natural herbal products are widely used in cosmetics, food supplements or pharmaceutical products. The market is constantly changing, with new references, new formulations, new plant species, and each country provides guidelines aiming at verifying the authenticity of plant raw materials, incl. Pharmacopoeias. Faced with this expansion of the market, it is difficult to change these standards quickly enough. Today, many of these methods are outdated or limited and can no longer guarantee adequate control. Therefore, despite these available references, many falsifications are found on the products on the market **[1]**. Fraud can be, for example, confusion of species, voluntary mixtures of other species, significant dilutions, or enrichments by synthetic substances. It is within this framework that BotaniCERT, a plant analysis laboratory, analyzes many samples from the market to verify the authenticity of plant raw materials. Herein, the goal is to develop a unique and simple methodology to detect and anticipate all types of fraud while verifying the identity of botanical species with the highest possible level of confidence. It is necessary to consider the qualitative and semi-quantitative aspects of all detected substances. The first step of this project is to develop a methodology by UHPLC-DAD-MS with manual structural elucidation of more than 1000 secondary metabolites in more than 500 plant species in front of an automated methodology by UHPLC-DAD-Q/Tof-MS with quick annotation of known metabolites by bioinformatics global approach **[2,3]** to highlight discriminating differences between all studied plant species.

References: [1] Gafner et al. J. Nat. Prod., 2023, 86, 460-472. **[2]** Nothias-Scaglia et al. Spectra Analyse, 2015, 307, 65-70.

Poster 24

Efficient semi-synthesis of a new 28-norlupane library with potential antiplasmodial activity

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Infectious diseases caused by protozoan parasites, remain as major health problems, affecting particularly developing countries. Among them, malaria caused by *Plasmodium sp*. and especially by *P. falciparum* is of great concern with 241 million clinical cases reported and 627 000 people killed in 2020.**[1]** Despite a major advance has been made recently, the necessity and the interest to find new active compounds is growing. In that context, "Nature" remains the main source of new prototypes for chemists, who are using the natural compounds themselves or modifying them to create new drugs.

Previous work in the laboratory, carried out on *Dipterocarpus costatus* Gaertn.f. (Dipterocarpaceae), led to the isolation of an antimalarial hit compound: a new endoperoxide 28-norlupane **(1)** which showed potent *in vitro* activity against *Plasmodium* sp.**[2]** Since its endoperoxide 28-norlupane possesses both a lupane backbone and an endoperoxide function, it appears interesting to go on studying for its antiplasmodial activities. However, norlupanes contents are low in the plant source, which is furthermore a protected species of the rain forest of Thailand. To get access to these kind of structures, semisynthesis route seems very promising.

In this project, we designed an efficient semisynthesis of the active endoperoxide from betulinic acid, the latter being readily available in high amount from the exfoliating bark of plane tree (*Platanus acerifolia*), a common sustainable and renewable natural source, in order to evaluate its mechanism of action and establish structure-activity relationships.

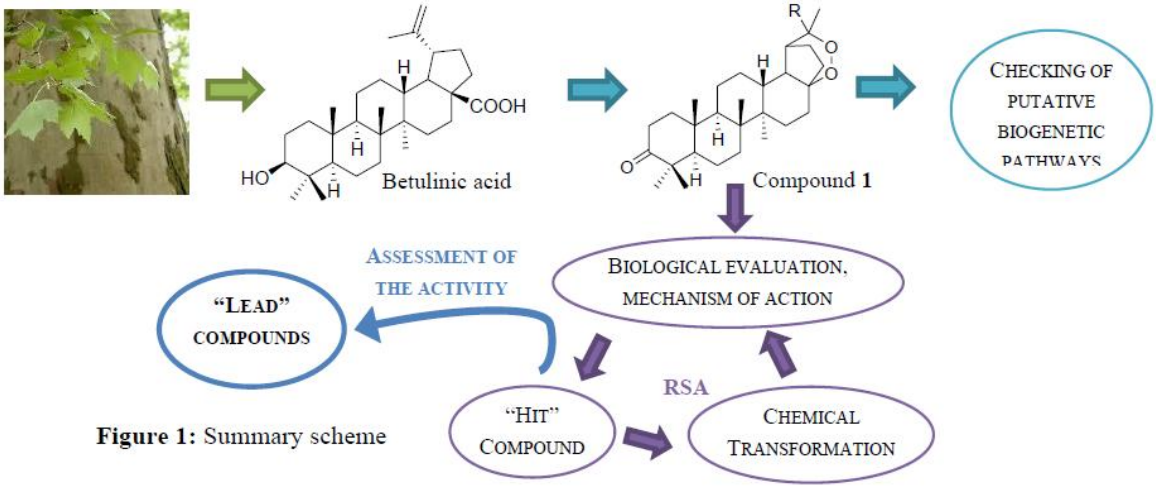

Figure 1: Summary scheme

References: [1] World malaria report 2021. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO. **[2]** PhD thesis of Malaï SATIRAPHAN, University Paris-Descartes/University SILPAKORN (27/09/2012)

Poster 25

Apoptotic agents from the Endolichenic fungi against chemoresistant cancers

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Globally, cancer is a major cause of death, with breast, lung, and colon cancers being the most common. Chemoresistance is a significant hurdle in cancer treatment. Endolichenic fungi, non- pathogenic fungi located in lichens, offer a hopeful solution in the search for new bioactive compounds with anticancer potential[1,2].

The Endolichenic fungi (ELF) were previously isolated from lichens collected in Nouvelle Aquitaine Region (France). The objective is to highlight the antiproliferative potential of the Endolichenic extracts and their metabolites against colorectal cancer (HT-29) and triple-negative breast cancer (MDA-MB- 231). Extracts were obtained after the cultivation of ELF strains on 3 media on a small scale.

Screening of 20 Endolichenic extracts against chemoresistant cell line HT-29 highlighted their antiproliferative potential with IC_{50} values ranging from 2 to 60 µg/mL (MTT Test). EtOAc extracts of PA08S and XC04P were the most active with IC_{50} values lower than 6 µg/mL.

Solid state fermentation (10 L, SAB) of PA08 produced 5 g of EtOAc extract. Its Liquid-liquid extraction offered two fractions. The evaluation of their antiproliferative activity showed that hexane fraction has moderate activity with an IC_{50} of 16µg/mL and methanol fraction has an IC_{50} = 3µg/mL. The LC-MS/MS analysis of extract and fractions reveals very few matches in the MS database.

The bioactive compounds are currently being isolated, and their bioactivity will be tested through apoptosis studies on MDA-MB231 and HT-29 cells.
Conflict of interest: the authors declare no conflict of interest.

References: **[1]** Kellogg *et al.* , *Phytochem Rev*, **2017**, (16), 271-293 ; **[2]** Lagarde *et al.*, *Microbiol. Res.,* **2018** (211) 1-12

Poster 26

Co-culture of two fungi isolated from a lichen: potential source of antimicrobial metabolites.

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Despite significant advancements in scientific research, the microorganisms that colonize holobionts, such as lichens[1] like *Rhizocarpon geographicum*, remain largely understudied and unfamiliar. Holobionts represent complex symbiotic systems consisting of diverse microorganisms[2]. Despite their potential, these microorganisms have not been extensively investigated, leaving a vast reservoir of untapped potential in the form of bioactive specialized metabolites. These metabolites hold great promise for exhibiting a wide range of biological activities, including antimicrobial properties.
Considering the urgent global concern of antibiotic resistance and the pressing need for novel antibacterial compounds, exploring the microbial communities associated with holobionts becomes a matter of great importance. By studying the chemical profiles and ecological interactions of these overlooked microorganisms, we have the opportunity to discover a wealth of bioactive compounds that can contribute to the development of innovative antimicrobial agents.

Previous studies on fungi isolated from this lichen[3] and the potential of co-culture to activate critical genes and trigger the expression of novel molecules[4] have laid the foundation for our current research. In this study, we focus on two fungi, *Melanconium hedericola* and *Coccinonectria rusci,* both isolated from *Rhizocarpon geographicum*. The selection of this fungal pair is attributed to their involvement in an antibiosis zone, which was observed during the preliminary isolation stages. Moreover, these fungi have received little attention regarding their chemical aspects, indicating that they remain largely unknown and understudied. To address this knowledge gap, our mycochemical study involved multiple methods of culture, extractions, fractionations, and chemical profiling of these two fungi cultivated individually or in co-culture. Through this approach, we successfully isolated and identified numerous metabolites (belonging to quinazolinone, isocoumarin, xanthone … classes) derived from each fungus in both mono-culture and co-culture conditions. Furthermore, this study allowed us to examine the behavior of these fungi in liquid and solid media, providing valuable insights into their growth patterns and metabolic activities.
We are currently conducting tests to determine the antimicrobial activity of the isolated compounds. This evaluation will provide valuable information about their potential effectiveness against harmful microorganisms such as *Staphylococcus aureus* or *Pseudomonas aeruginosa*.

[1] D. L. Hawksworth et al., *New Phytol.*, 2020, 227(5), 1281-1283, doi: 10.1111/nph.16630.
[2] J.-C. Simon, *Microbiome*, 2019, 7(1), 5p doi: 10.1186/s40168-019-0619-4.
[3] A. Miral, « Microbiote de l'holobionte lichénique *Rhizocarpon geographicum* : étude de la diversité et applications biotechnologiques », Thèse, Rennes 1, 2022. [En ligne]. Disponible sur: https://www.theses.fr/s211215
[4] S. Bertrand *et al.*, *J. Chromatogr. A*, 2013, 1292, 219-228, doi: 10.1016/j.chroma.2013.01.098.

Poster 27

Discovery and design of active molecules from Gabonese plant biodiversity to fight neglected tropical diseases.

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Throughout the past decades, annonaceous plants have been of particular interest to the natural product community because of their therapeutic value and their richness in isoquinoline alkaloids **[1]**. Taking advantage from our laboratory historical collection of these compounds, a MS/MS database of 322 isoquinolines and other metabolites from Annonaceae was implemented and named IQAMDB **[2]**. The present communication describes the dereplication of known alkaloids from stem barks of *Greenwayodendron suaveolens* (Engl. & Diels) Verdc leveraging IQAMDB-informed feature-based molecular networking further refined by a Tima-R based *in silico* annotation and taxonomic weighting **[3]**. This strategy enabled the efficient annotation of more than 30 compounds and streamlined the isolation of a seemingly new lactam-containing sesquiterpene indole alkaloid (**1**). Upon structure elucidation, this compound turned out to be a diastereoisomer of greenwaylactam A (**2**), an original Witkop-Winterfeldt oxidized sesquiterpene indole alkaloid reported in 2021 from *G. oliveri* **[4]**. A cursory examination of the spectroscopic data of **2** revealed inconsistencies with the proposed structure appealing for a critical reappraisal. As a way to decipher this discrepancy, a targeted-isolation strategy was deployed towards all the accessible diastereoisomers of **1**. Two new molecules of the indole sesquiterpene alkaloid type were discovered, one of which turned out to be a diastereomer **3** with NMR data similar to greenwaylactam A (**2**).

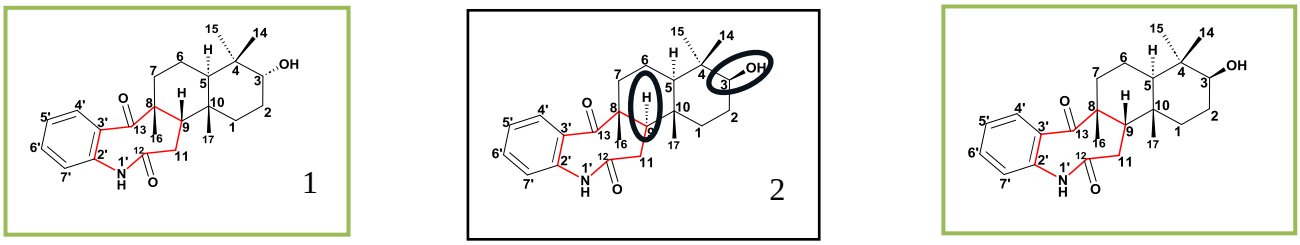

Figure 1 : Chemical structure of o new isolates from G. suaveolens *and comparison with the claimed structure of greenwaylactam A described from* G. oliveri*.*

References: [1] Attiq, A; *et al. Front. Pharmacol.* 2017. **[2]** Agnès, S. et *al*. *Sci. Data*. 2022**. [3]** Rutz, A, et al. *Frontiers in plant science.* 2019**. [4]** Kemgni, M. et *al*. *ChemSelect*. 2021.

Experimental evaluation of MS/MS spectra similarity indices using Monoterpene Indole Alkaloids

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Comparing two molecules to see how similar they are is an important issue for chemists. Such comparisons are used to detect new molecules, classify known molecules with respect to their potential use, etc. Overall, two types of information may be used to compute similarities between molecules: information on their atomic structures or information obtained from their analytical read-outs such as their tandem mass spectrometry (MS/MS) and/or their NMR spectra. Our study aims to evaluate the performance of the Morgan/Tanimoto coefficient **[1]**, modified cosine, Spec2Vec **[2]**, and MS2Deep Score **[3]** similarity indices to measure structural and spectral similarities between molecules. To illustrate this evaluation, we used MIADB **[6]**, an MS/MS database dedicated to the emblematic monoterpene indole alkaloids and the indices as implemented in the Python library MatchMS **[4]** and RDkit **[5]**. This study provided evidence that modified cosine was able to capture the structure similarity from the spectral comparison in a very efficient manner, with respect to the MIA skeleton classification.

References: [1] Morgan and Harry., *J. Chem. Doc*., 1965, 5, 107-113.
[2] Huber, *et al*., *PLoS comput. biology*., 2021, 17, e1008724.
[3] Huber, *et al*., *J. Cheminformatics*., 2021, 13, 1-14.
[4] Huber, *et al*., Python library., 2020.
[5] Landrum and Greg., Rdkit documentation., 2013, 1, 4.
[6] Ramos *et al*., *Sci. Data*., 2019, 6, 15.

Poster 29

Exploring the chemical diversity of essential oils in Armenian markets: a comprehensive analysis of composition profiles

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Due to its location at the convergence of multiple biogeographical regions, Armenia experiences significant variations in climate and soil conditions, resulting in a diverse range of plant chemotypes [1]. However, there has been a lack of recent reports on the biological activity of plants found in Armenia's flora. There are few with well-described essential oil profiles, despite the vast biodiversity of Armenian flora. This study aimed to analyse the chemical composition of essential oils used by the population and found in the Armenian market. Unfortunately, only essential oils of foreign origin can be found. Three essential oils, *Lavandula angustifolia*, *Abies sibirica*, and *Rosmarinus officinalis*, were selected, and analysed by GC-MS and GC-FID. Based on a comparison with relevant literature and prior GC analyses, it was found that the essential oil of *Lavandula angustifolia* product exhibited similar chromatogram to *Lavandula x intermedia* "Grosso", mainly because of the high amount of camphor (6.98%). The presence of camphor in essential oil product should be controlled due to its toxicity for children and toddlers. Camphor poisoning, frequently seen in Asian children due to the lack of strict regulations on this monoterpene, can occur through ingestion or skin contact. Recent case reports indicate that all patients required medical treatment, exhibited leucocytosis, and two experienced hyperglycemia [2]. The GC of the essential oil of *Rosmarinus officinalis* showed some similarities with a *Rosmarinus officinalis* chemotype cineol profile, with a surprising higher amount of α-pinene (24.86%) and β-pinene (10.62), compared to the cineol amount (19.51%). In contrast, the GC of the *Abies sibirica* conformed to the classical standards. These data are very important for a safe and therapeutic use of these essential oils.

References:

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2. Wojtunik-Kulesza, K.A., 2022. Toxicity of Selected Monoterpenes and Essential Oils Rich in These Compounds. *Molecules* 27, 1716. https://doi.org/10.3390/molecules27051716

Poster 30

SPECIALIZED METABOLITES WITH ANTIVIRAL PROPERTIES FROM A VIETNAMESE PLANT: ISOLATION AND SYNTHESIS

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The plant metabolites group at the Institute of Chemistry of Natural Substances (ICSN) aims to study and valorize specialized metabolites isolated from plants. For that, the plant extract library named Extractothèque ICSN, containing more than 15,000 extracts, is regularly screened by biologist partners. Recently, a selection of 1650 plant extracts from Extractothèque ICSN was evaluated on an inhibition cell-based assay on human Coronavirus (HCoV-229E and SARS-CoV-2). The EtOAc and MeOH extracts of the leaves of the Vietnamese species *Melodorum fruticosum* were selected for their good activity on HCoV-229E. Bio-guided fractionation led to the isolation of 14 pure products, including 3 novel compounds. Their antiviral evaluation confirmed the interest of some metabolites with IC_{50} around 6 nM for toussaintine C. To validate their activity and improve our knowledge of the structure-activity relationships, we performed the total synthesis of toussaintine C and developed a divergent synthesis of analogs.

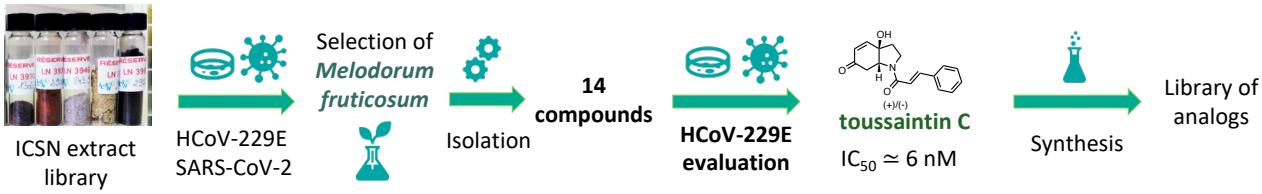

Figure 1: The scheme of the project procedure

Poster 31

TOWARD NATURAL INHIBITORS OF CARBAPENEMASES

RAMON MARTINEZ Isabel [1*], OUESLATI Saoussen [2,3], APEL Cécile [1], NAAS Thierry [2,3], LITAUDON Marc [1], DESRAT Sandy [1] and ROUSSI Fanny [1]

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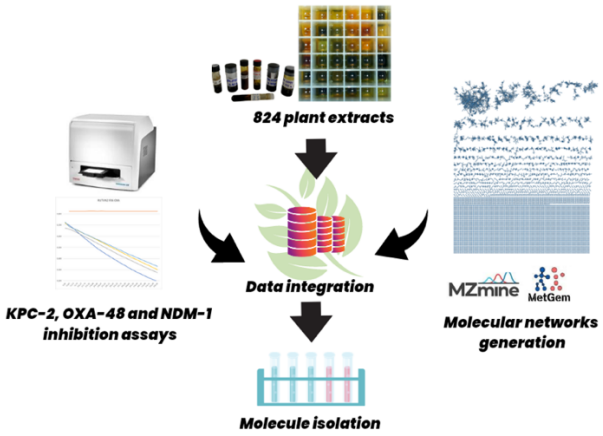
The threat of antibiotic resistance is more than ever present in our society and will soon become the main cause of death worldwide. Three carbapenem-resistant bacteria are classified by the World Health Organization (WHO) as the most compelling in the race to develop new therapeutic solutions. Carbapenemases are a type of enzyme synthetized by a large number of these bacteria which hydrolyze the beta-lactame core of the antibiotic structure, thus inactivating it. This represents nowadays one of the main mechanisms responsible for the degradation of this type of large spectrum antibiotics.

In this context, a library of 824 plant extracts from rich biodiversity world areas (Malaysia, Vietnam, and New Caledonia), was screened against three of the main existing carbapenemases (KPC-2, OXA-48, NDM-1) to find natural inhibitors of these enzymes. The method employed for this screening is based on a measure of the decrease in the optical density of imipenem (a carbapenem antibiotic) when adding the hydrolyzing enzyme. This decrease is slowed or interrupted in the presence of a carbapenemase inhibitor.

This screening ended up in the selection of five plant extracts with high and reproductible activity profiles inhibiting two of the three tested carbapenemases. Among this selection, *Fissistigma litseaefolium,* a Malaysian tree species, was selected for further analysis, due to the high activity showed by both bark and leaf extracts. A bioactivity and mass-guided isolation of the potentially active molecules, combined with molecular networking analysis to obtain a clear visualization of taxonomical data and distribution of the activity between species, is now being conducted to identify the compounds responsible for the inhibitory activity.



Poster 32

Combining innovative electrochemical and *in vitro* models to assess the toxicity of environmental furanic compounds

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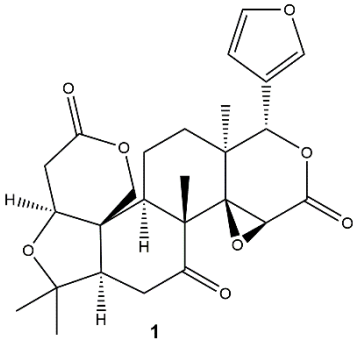
The presence of furanic compounds of both plant and fungal origin in the environment constitutes a significant risk of liver toxicity following the ingestion of plants and, more generally, any food likely to contain them. **[1]** This hepatotoxicity is associated with metabolic bioactivation by cytochromes P450 (CYP450) and can range from enzymatic inhibition or reversible toxic hepatitis to hepatic carcinoma. The increasing consumption of plants for health purposes, and the constant increase in mycotoxin levels due to global warming make this threat a major current and future health issue. In this context, it is essential to have effective study models to predict the toxicity of such compounds and to establish the safety of both plants and foods containing them in complex mixtures. In addition, there is a very large chemical diversity of furan molecules that may participate in the "natural" human chemical exposome and the great majority of these compounds are not commercially available. Therefore, no systematic evidence of structure-toxicity relationships has been established in these furan series. Furthermore, the assessment models used so far are generally complex and expensive, and the evaluation of the potential toxicity of furanic compounds relies on the detection of adducts formed with endogenous nucleophiles such as glutathione in cell and even animal models. **[2, 3]**

The aim of our work **[4]** is to develop a simple electrochemical model that will mimic the oxidation of furans by CYP450 and thus the metabolic activation responsible for toxicity, in order to study their potential toxicity. It will enable the toxicity of these compounds to be predicted from their oxidation susceptibility (oxidation potential value). This model could be correlated with an original *in vitro* biological model using human liver HepaRG cells that overexpress CYP450 at a level comparable to that of human hepatocytes in primary culture, and which will consist of studying the inhibition of the activity in particular of CYP3A4 generally involved in the metabolism of furans.

Preliminary results obtained with structurally complex limonin (**1**), used as model molecule of CYP3A4 inhibitor, will be presented herein.



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References: [1] Cachet X., *et al. Sci Rep.* 2018, 8:13520. **[2]** Li H., *et al. Adv. Mol. Toxicol.* 2016, 10:55-97. **[3]** Tian M., *et al. Drug Metab. Dispos.*, 2022, 50:655-670. **[4]** PhD thesis of K. Sisouklath, University Paris Cité, defended on June 28, 2023.

Poster 33

COMBINING LACCASE-MEDIATED DIMERIZATION OF RESVERATROL AND CENTRIFUGAL PARTITION CHROMATOGRAPHY: OPTIMISATION OF *E*-LABRUSCOL PRODUCTION AND IDENTIFICATION OF NEW RESVERATROL DIMERS.

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Resveratrol dimers are of great interest for pharmaceutical and cosmetic applications. Nevertheless, the yield of their bio-production is limited by both the competition between the possible radical-radical coupling pathways and complex isolation procedures. Alternative organic synthesis methods do not afford higher yields. Although enzymatic routes can provide dimers in one step from resveratrol, bio-catalysis optimisation is required to improve yields and orient radical-radical coupling selectivity toward a specific resveratrol dimer, *E*-labruscol herein. After a rapid study of the relative importance of the bio-catalysis parameters, a design of experiments was implemented to produce *E*-labruscol in high yield by laccase-mediated dimerization of resveratrol. *E*-labruscol and δ-viniferin were identified and isolated by flash chromatography as major products in 21% and 52% yields, respectively. As an alternative to purification on silica gel, an efficient separation of the aforementioned compounds was achieved by centrifugal partition chromatography (CPC) (Figure 1). This technology provided δ-viniferin in 63.1% yield (90% purity) and labruscol isomers in 20.4% yield with a purity of 95% after a CPC polishing step, but it also revealed the presence of *E*-labruscol diastereomers, leachianol F and leachianol G, as major reaction products, as well as less abundant products: pallidol, Z-labruscol, ε-viniferin and two new resveratrol dimers named iso-δ-viniferin and iso-ε-viniferin. **[1]**

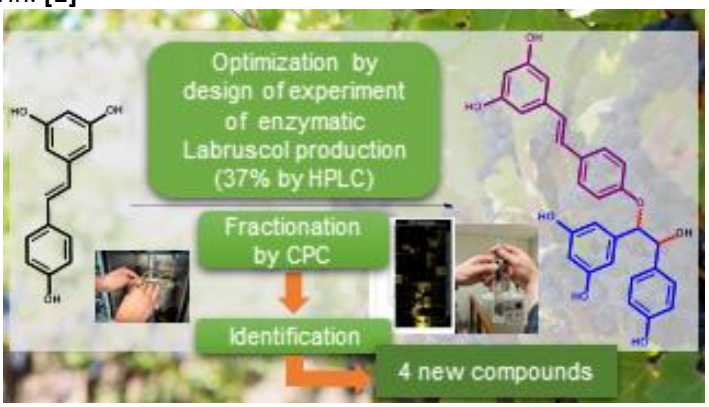

Figure 1: Challenging synthesis and purification of the valuable dimer of resveratrol *E*-Labruscol were optimized. Additionally, 4 new resveratrol dimers were identified

References: [1] Sursin et al., ACS Sustainable Chemistry & Engineering, 2023, *in press*

Poster 34

Discovery of the First Natural Trimeric Monoterpene Indole Alkaloid from *Catharanthus roseus*

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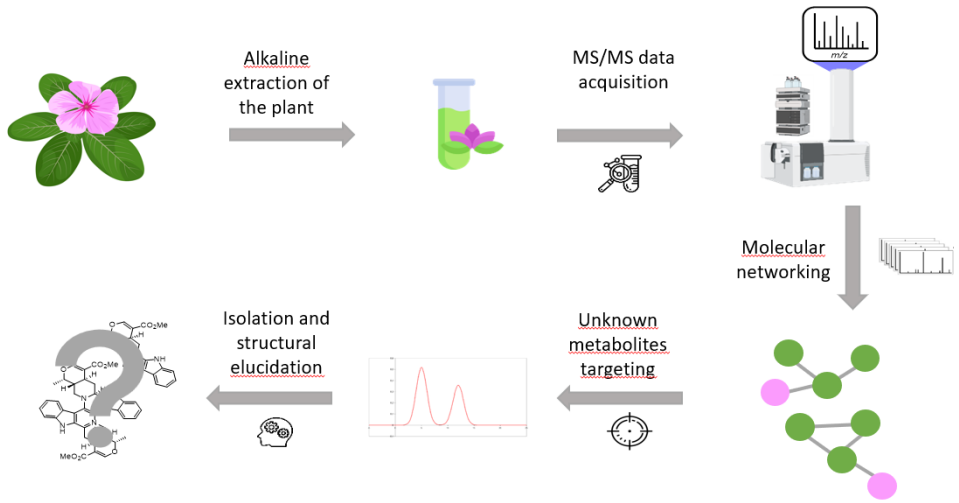
Catharanthus roseus (L.) G. Don, also known as the Madagascar periwinkle, is one of the most well-studied plants of the Apocynaceae family owing to its remarkable therapeutic properties (used in traditional medicine to treat diabetes, malaria or even skin diseases). This plant is also deemed for its wide chemical diversity, as *Catharanthus roseus* is known for producing more than 130 monoterpenoid alkaloid whose biosynthetic pathways have been extensively studied[1], comprising vinblastine and vincristine, two illustrious spindle poisons used as cancer treatment.
With the recent emergence of new chemoinformatic tools[2] (such as molecular networks or MS/MS spectra prediction tools) and the development of numerous open-access spectral databases (LOTUS[3]), targeting unknown secondary metabolites in complex natural extracts is becoming an easier task.
For several years now, our laboratory has committed to enhancing the value of its heritage by reexploring the therapeutic potential of the numerous plants and extracts in our collections. In this context of reinvestigation of the laboratory's legacy, our team decided to confront the MS/MS dataset of a *Catharanthus* roots extract to different annotation tools to reinvestigate the chemical space of this renowned plant. This study led us to the discovery of an intriguing trimeric monoterpene indole alkaloid that we were able to isolate and fully-characterize through 1D and 2D NMR studies and TD-DFT calculations. This newly characterized metabolite exhibits two unprecedented inter-monomeric bridges together with an unreported *seco*-ajmalicine unit.

Figure 1: General workflow of isolation



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Poster 35

MISE EN EVIDENCE DE STILBENES OLIGOMERISES A POTENTIEL ANTIFONGIQUE DANS LES CO-PRODUITS DE LA VIGNE PAR UNE APPROCHE DE METABOLOMIQUE NON-CIBLEE

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Fusarium graminearum est un champignon filamenteux pathogène des cultures céréalières et est le principal agent responsable de la contamination des récoltes par des mycotoxines de la famille des trichothécènes de type B. Compte tenu de la dangerosité de ces mycotoxines pour l'Homme et les animaux, une bonne gestion des cultures est indispensable pour limiter la contamination des céréales ; un des leviers de cette gestion repose sur l'utilisation de fongicides de synthèse. Afin de développer des approches plus durables, l'utilisation de métabolites d'origine végétale possédant des propriétés antifongiques est une piste envisagée **[1]**. Dans cette étude, des co-produits de la filière viticole, riches en composés phénoliques, ont été criblés pour leur activité antifongique vis-à-vis de *F. graminearum*. Treize éco-extraits de bois de vigne issus de différents cépages ont été obtenus, puis testés in vitro en présence du champignon afin d'évaluer leur potentiel antifongique. La composition chimique des extraits a été analysée par UHPLC-HRMS^n. Afin de cribler les métabolites bioactifs, une approche par métabolomique non-ciblée exploitant les données de LC-MS^n a été déployée, s'appuyant sur des analyses multivariées et la génération d'un réseau moléculaire basé sur la bioactivité **[2]**. Ainsi, des stilbènes oligomérisés ont été mis en évidence comme étant de possibles molécules antifongiques. Ces travaux soulignent le potentiel des co-produits de la filière viticole comme source de polyphénols à activité antifongique, et témoignent de l'efficacité de la métabolomique non-ciblée couplée à des essais biologiques pour détecter des molécules bioactives.

Références : [1] Ahmed *et al., Compr. Rev. Food Sci. Food Saf.*, 2022, 21, 1161-1197. **[2]** Nothias *et al.*, *J. Nat. Prod.*, 2018, 81, 758-767.

Poster 36

PROPRIETES ANTI-INFLAMMATOIRES DE LA TEINTURE MERE D'*ARNICA MONTANA* SUR DES MODELES CELLULAIRES *IN VITRO*

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Introduction : *Arnica montana* L. est une plante vivace avec des propriétés anti-inflammatoires et antalgiques.(1) La teinture mère (TM) d'*Arnica montana* est préparée à la teneur en éthanol de 45 % (V/V), à partir de la plante entière fleurie fraîche *Arnica montana* L., selon la monographie de la pharmacopée française pour préparations homéopathiques.(2) La plante provient de différentes zones géographiques et peut être d'origine sauvage ou cultivée. La congélation de la plante fraîche d'*Arnica montana* L. permettrait de maintenir un approvisionnement continu malgré les contraintes environnementales (sécheresse, pollution…) qui menace cette espèce protégée. **Objectifs du projet : 1-** Etudier l'impact de la préparation des lots de TM d'Arnica montana à partir de plante fraîche ou congelée **2-**Etudier l'impact de l'origine géographique et de la méthode de culture pour la fabrication des TM d'Arnica montana **3-**Etudier la conservation des lots de TM (différentes durées de conservation). **a)** sur les principaux composants des lots de TM d'Arnica montana **b)** sur l'effet anti-inflammatoire des lots de TM d'Arnica montana sur deux modèles cellulaires (cellules endothéliales et microgliales). **Résultats :** Les différents lots de TM présentent un profil CCM caractéristique d'Arnica en accord avec la pharmacopée française(2) et indiquent notamment la présence de flavonoïdes et d'acides phénoliques. Dans les cellules endothéliales, tous les lots de TM d'Arnica montana (ancien, nouveau, frais, congelé, sauvage et cultivé) diminuent significativement la production d'ICAM-1 par rapport au véhicule (A45) Dans les cellules microgliales, tous les lots de TM d'Arnica montana diminuent la production d'IL-6 et de MCP-1 par rapport au véhicule (A45) mais des effets différents liés à la durée de conservation (ancien vs nouveau), de la congélation (frais vs congelé) et de la culture (sauvage vs cultivée) sont observés. **Conclusion :** La composition des lots de TM d'*Arnica montana* est comparable selon la durée de conservation et l'origine géographique en France. Le procédé de congélation de la plante entière fleurie *Arnica montana* L. n'affecte pas de manière significative le profil caractéristique. Les lots de TM d'*Arnica montana* provenant de plante fraîche ou congelée conservent leurs propriétés anti-inflammatoires.

Références : **[1]** Iannitti *et al*. Effectiveness and Safety of *Arnica montana* in Post-Surgical Setting, Pain and Inflammation. Am J Ther, 2016 23, e184–e197. **[2]** Arnica montana pour préparations homéopathiques. Pharmacopée française. Agence Nationale de Sécurité des Médicaments (ANSM), 2008

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