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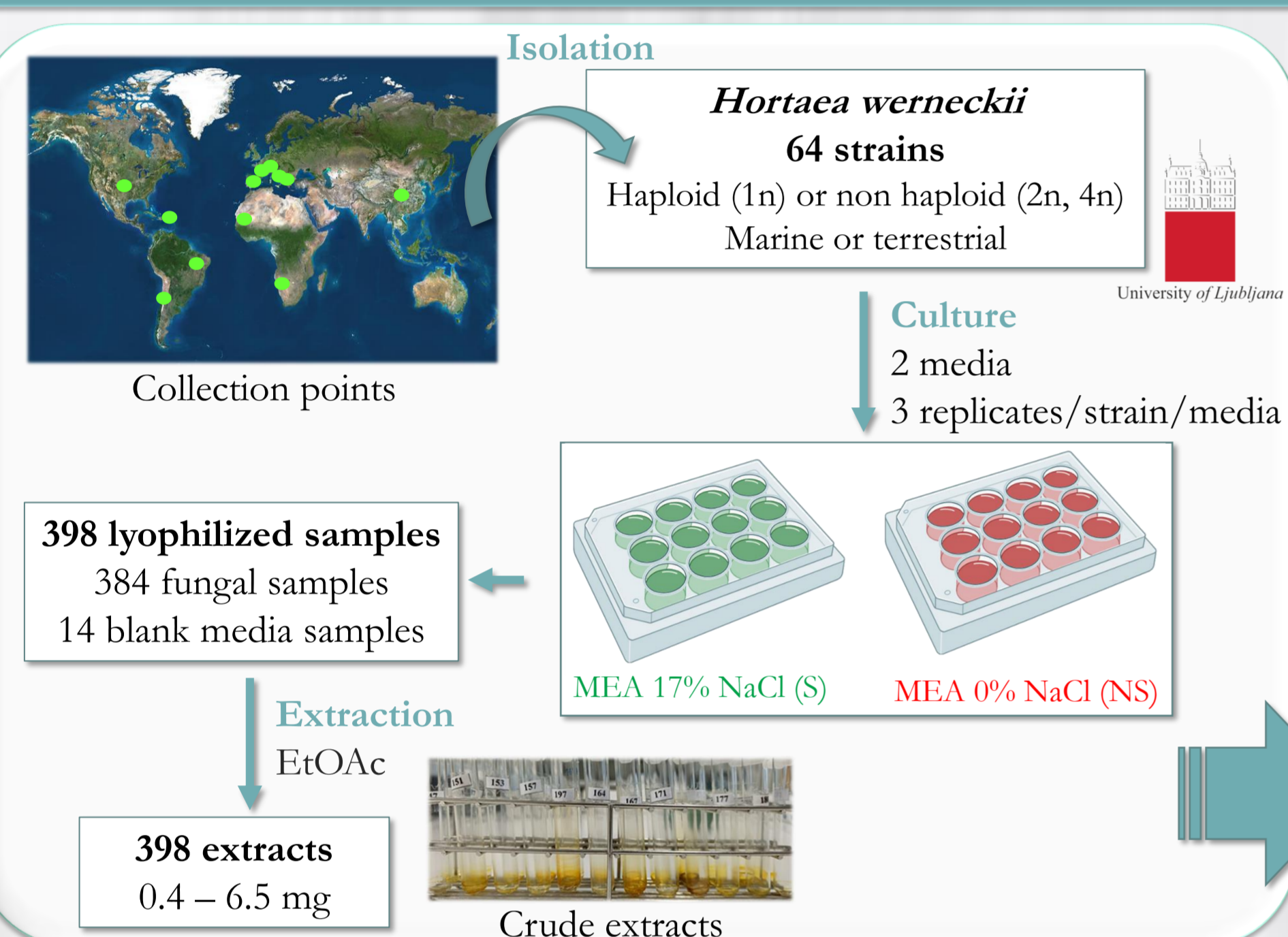
Background

Hortaea werneckii (Ascomycota, Dothideomycetes) is a filamentous 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 (only 3 metabolites isolated), making *H. werneckii* an interesting candidate for the discovery of new metabolites and bioactive molecules. On the other hand, Gostinčar *et al.* (2022) (University of Ljubljana) have conducted a large genomic study on this species, by sequencing 64 strains isolated from multiple environments around the world¹. This work led to a collaboration between our lab teams, in order to investigate the chemical diversity of the species and identify a possible relationship between the metabolomes and the genomes.

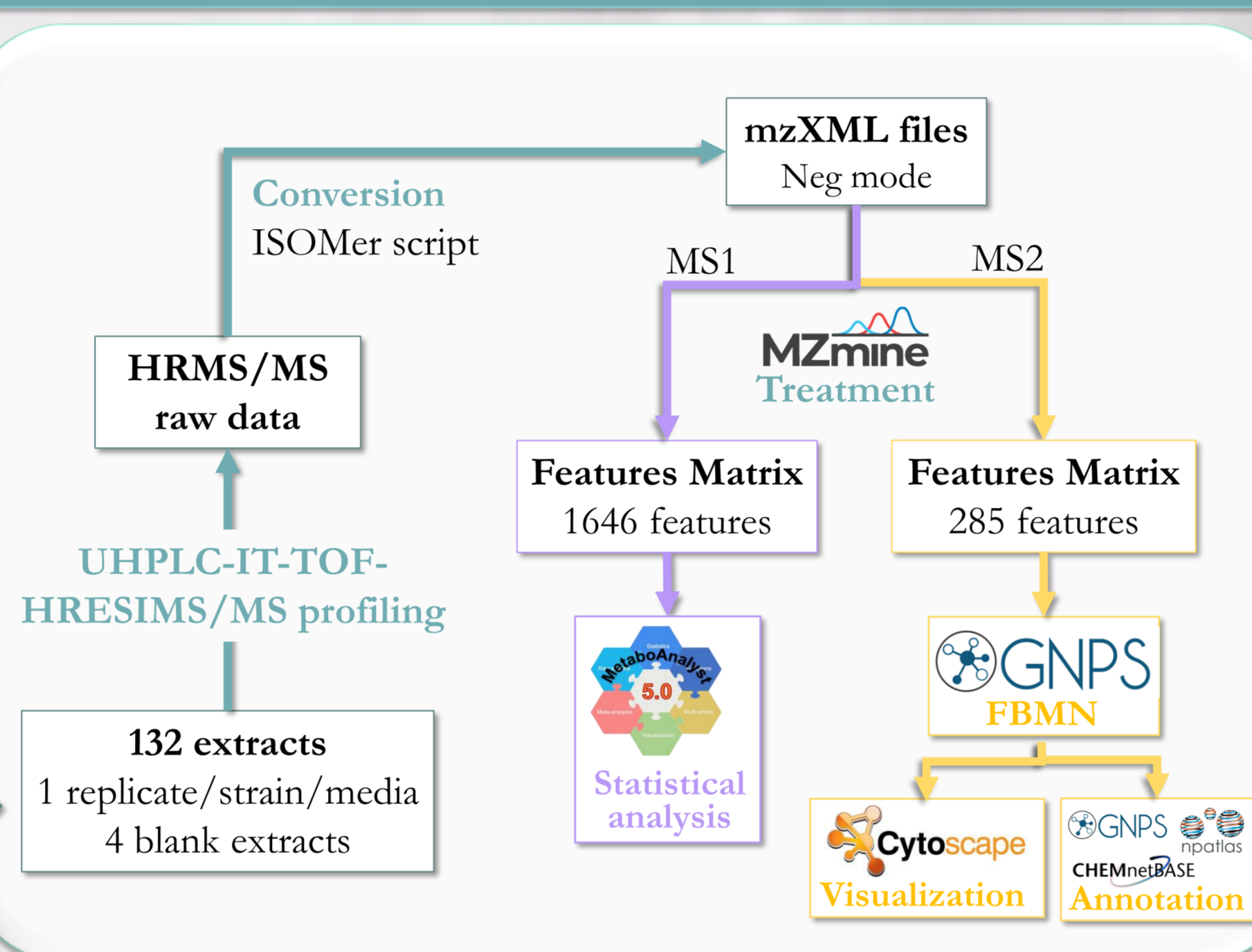
- Investigate the chemical diversity of the 64 sequenced strains through a metabolomic study.
- Highlight some interesting chemical entities.
- Identify a possible relationship between the metabolome and the genome of the strains.
- Isolate and identify new and bioactive compounds from the yeast.

Metabolomic study

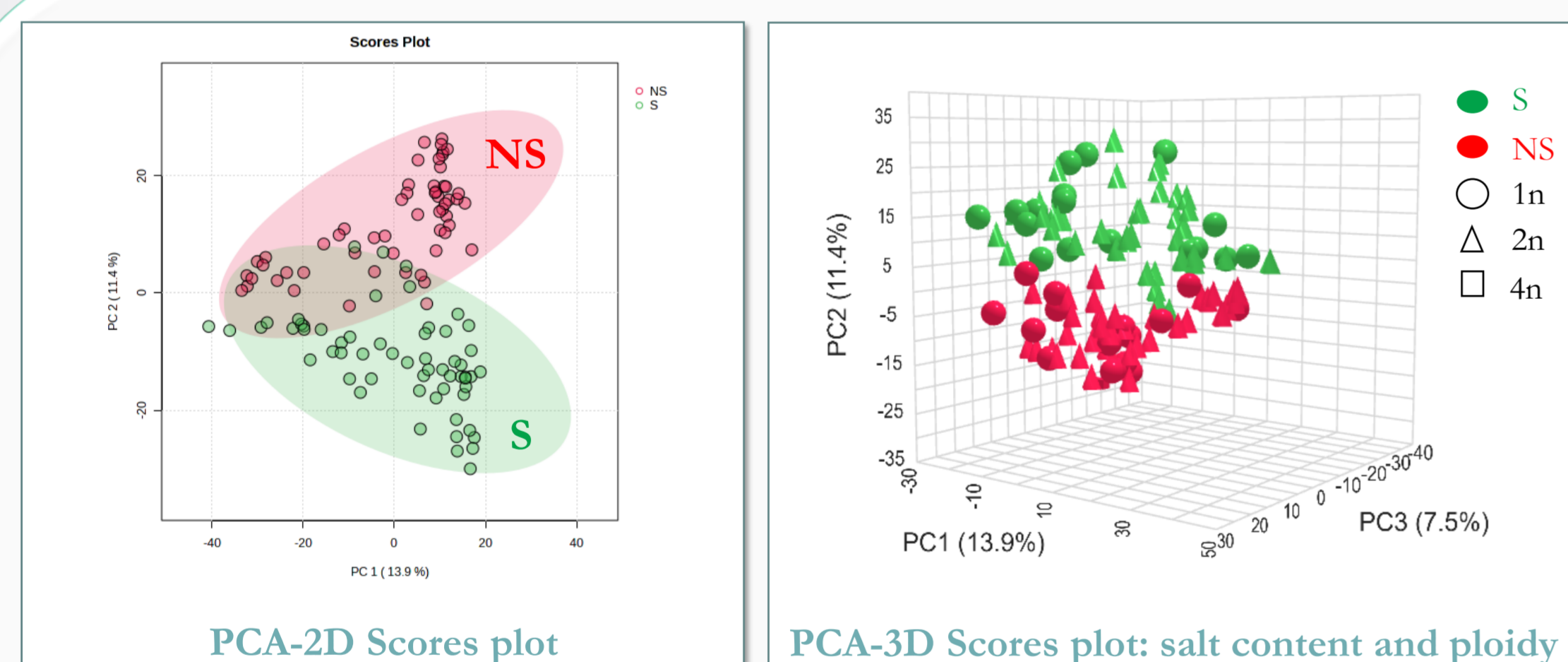
Samples preparation



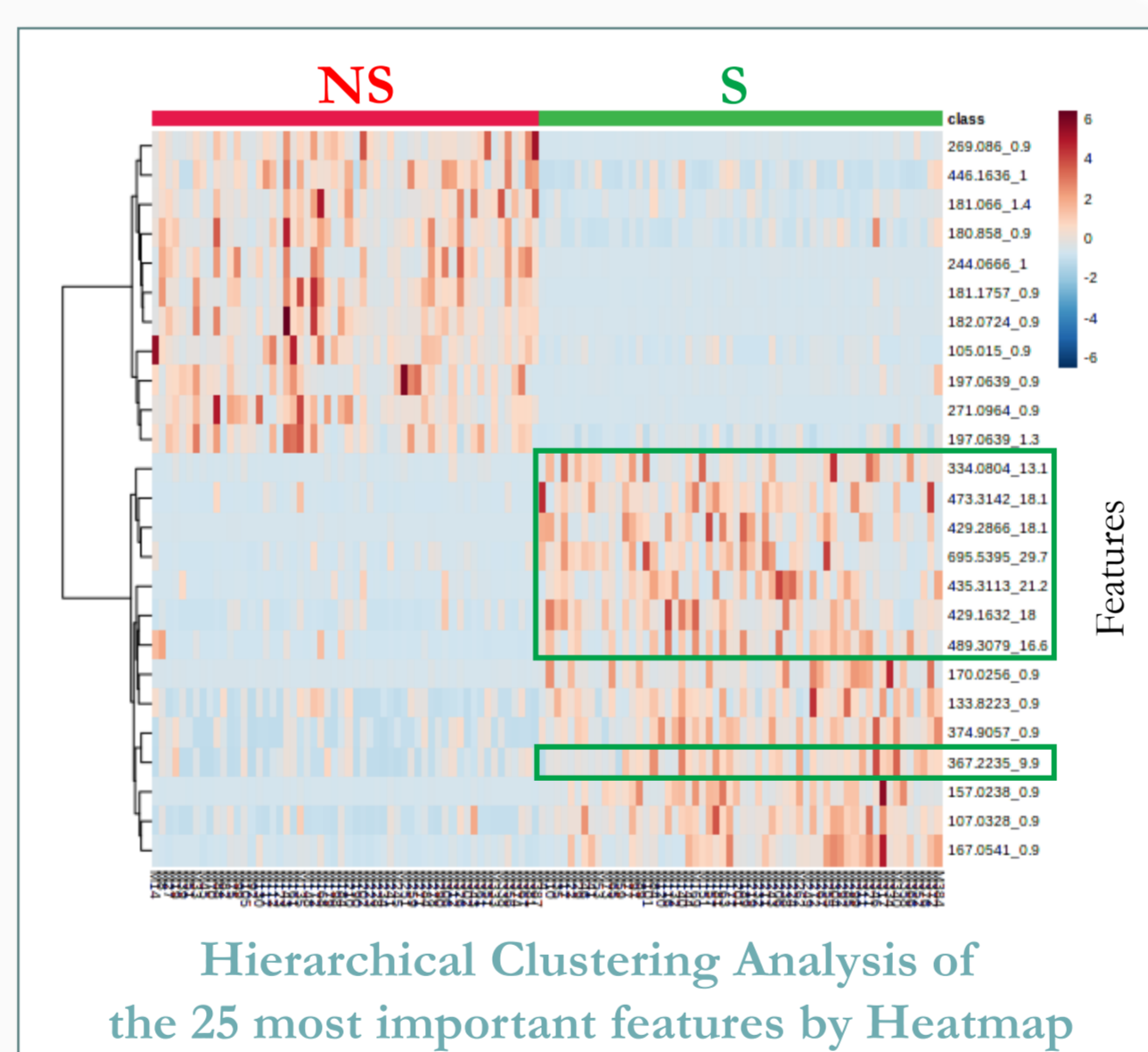
Data acquisition and treatment



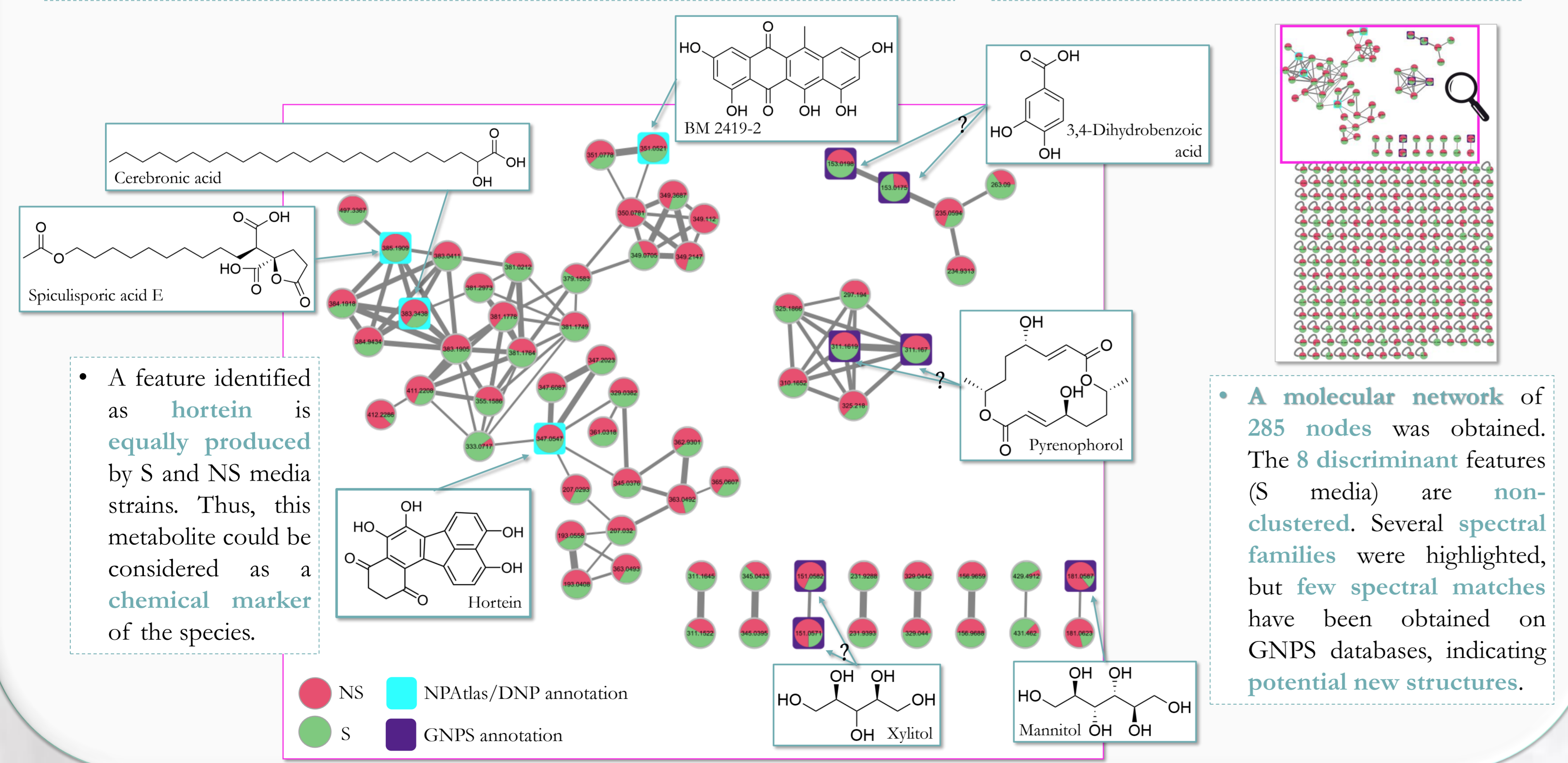
Statistical analysis and molecular networking



- The PCA highlighted two groups of samples: non-salt media samples (NS) and salt media samples (S).
- The 3D Scores plot again showed that most of the variability of the samples was due to the presence of salt in the media. Information addition about the ploidy level (different shapes) did not display any significant clustering according to this data. Similar results were observed with the habitat (marine/terrestrial) or continent where the strains were collected. Further investigations on other principal components could provide other meaningful information about the influence of the ploidy level or the habitat of the strains.



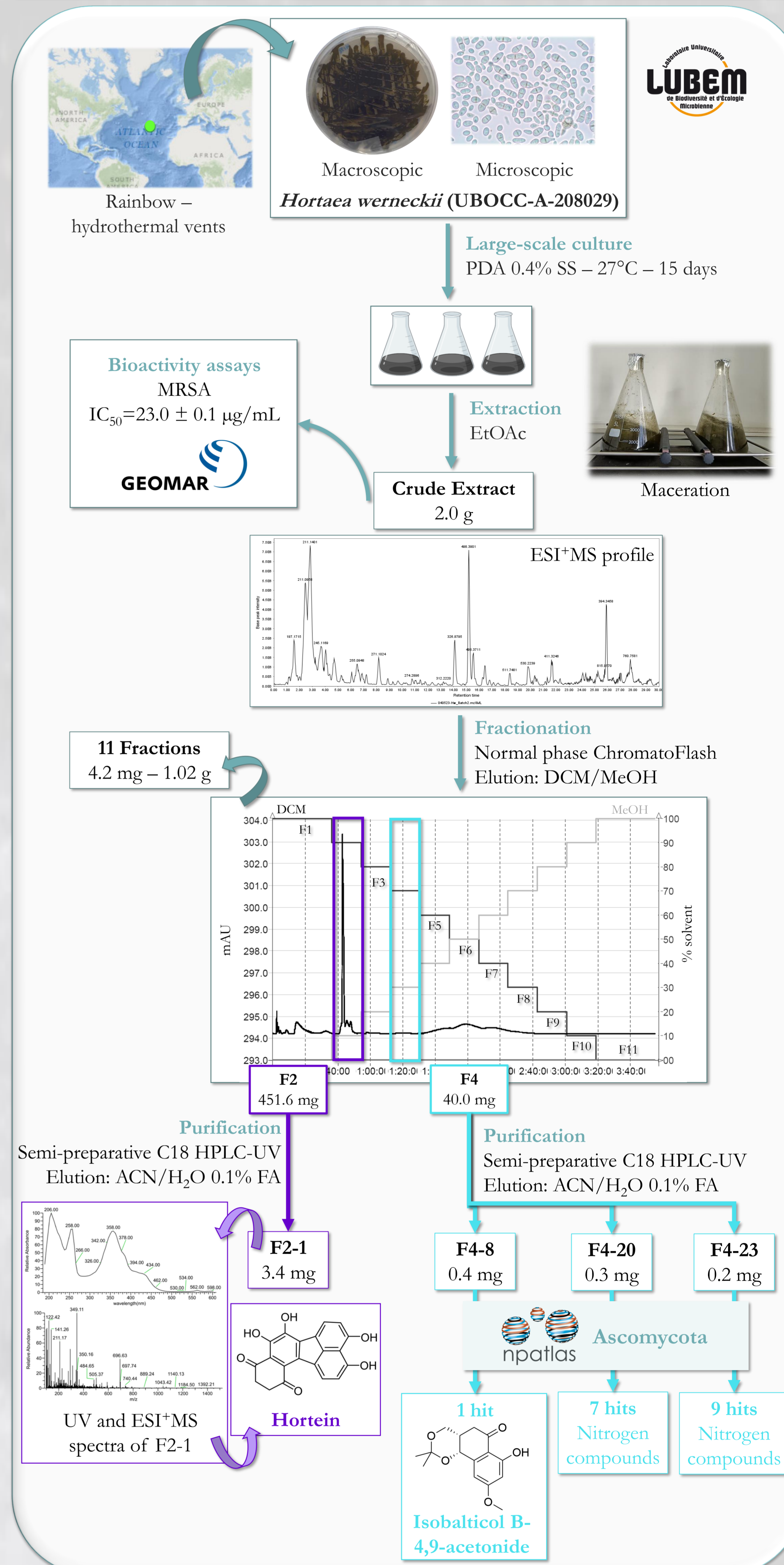
- Hierarchical clustering is presented for the 25 most important features for a better visualisation. 8 mid-polar to apolar (RT 9.9-29.7 min) and putatively identified features are highly produced in S media and absent in NS media.



- A feature identified as hortein is equally produced by S and NS media strains. Thus, this metabolite could be considered as a chemical marker of the species.

- A molecular network of 285 nodes was obtained. The 8 discriminant features (S media) are non-clustered. Several spectral families were highlighted, but few spectral matches have been obtained on GNPS databases, indicating potential new structures.

Compounds isolation



Conclusion & Perspectives

According to the metabolomic study,

- No relationship between the genomes and the metabolomes of the strains could be observed.
- The salt content in media is the main factor inducing a modulation of the strains metabolites production.
- The metabolites specifically produced in salt media are mid-polar to apolar, and should be isolated and identified.
- Hortein has been identified as an ubiquitous metabolite, and could be considered as a chemical marker of *Hortaea werneckii*.
- Several spectral families, including hortein analogues, have been identified on the molecular network.

In order to complete this work, the following perspectives are considered:

- Dereplication of features using ChromAnnot
- Large-scale culture on MEA 17% NaCl media
- Isolation and identification of the discriminant metabolites
- Obtention of hortein analogues in order to evaluate their biological activities and highlight a potential structure-activity relationship

From the strain grown on PDA media,

- Four metabolites were isolated.
 - One of them was identified as hortein based on MS and UV spectra.
 - Another was putatively identified as isobalticol B-4,9-acetonide.
- Thus, the following steps will be soon conducted:
- Identification of the isolated metabolites (HRMS, NMR)
 - Bioactivity assays on the isolated metabolites

References

1. C. Gostinčar *et al.*, *GigaScience*, 2022, 11, 1-16; 2. N. Gunde-Cimerman and A. Plemenitaš. *Rev. Environ. Sci. Biotechnol.*, 2006, 5, 323-331; 3. A. Marchetta *et al.*, *Life*, 2018, 8, 31; 4. N. Gunde-Cimerman *et al.*, *FEMS Microbiol. Rev.*, 2018, 42, 353-375; 5. I.V. Grigoriev *et al.*, *Nucleic Acids Res.*, 2014, 42, D699-D704; 6. K. Blin *et al.*, *Nucleic Acids Res.*, 2021, 49, W29-W35.

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