Catch the metabolomic fingerprint of a complex natural product and predict its quality!

This is the first work published so far, that shows the application of a comprehensive metabolomic fingerprint analysis to assure the production's quality of complex natural products, especially those based on medicinal plants. Natural products as medicinal plants have been used since ancient times in the folk medicine for treating a broad range of diseases. Although the last decade has witnessed a marked growth in the market of plant-based natural products, their high complexity in terms of composition still makes a challenging task the guarantee of quality, efficacy and safety requirements.

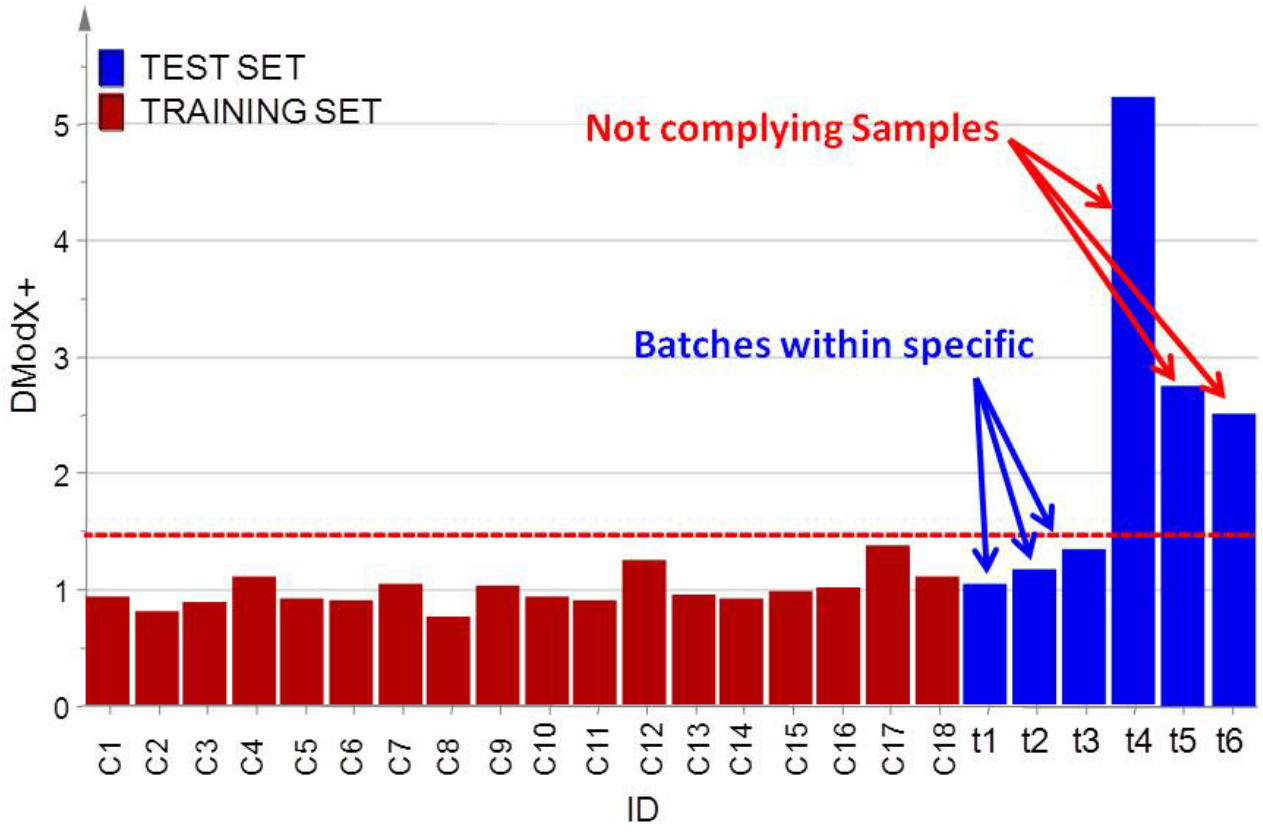

Fig. 1. DModX+ control chart (control limit equal to 95%); in red are reported the DModX+ of the samples of the training set within specific, while in blue the DModX+ of the predicted new samples three of which are not complying.

Before going into the core of the research results, we have to give some definitions: what is a natural product? The broadest definition of natural product is "anything that is produced by life", so natural products may be the extracts of cells, tissues, or the secretions of microorganisms,

plants and animals. A crude extract (or a coarse fraction) from any one of these sources will contain a huge number of structurally different and often novel chemical compounds as result of their metabolic processes. A natural product is also a selected blend of the above materials suitably prepared and mixed to achieve a formulation that can be of therapeutic benefit as medicine, food supplement, cosmetic or medical device.

Natural products are complex systems that have always been seen as difficult to analyze and to standardize. The historical approach used to analyze natural products that has been followed till now resulted in a simplification of the complex system with the analysis of few marker compounds and the standardization of the production process based on them.

We have found that by using mass spectrometry through an untargeted metabolomic analysis it's possible to take the sharpest fingerprint of a complex natural product that is used to assure its quality and batch to batch compliance. Metabolomic analysis by mass spectrometry is an effective tool to take information on a complex product as a system, as all the metabolites present can be specifically and selectively revealed through their own molecular mass.

What is a metabolomic analysis? Metabolomic is the technology that aims to identify and quantify the metabolome that is the complete set of small-molecule metabolites. Metabolomic analysis determines accurately even the slightest changes of molecular profile of an organism (whatever it is, vegetal or animal). So, it is understandable why a metabolomic analysis appears ideal for complex natural product analysis.

By an untargeted metabolomic analysis we can perform quality control of complex natural products taking the products fingerprint, including unknown metabolites. As Metabolomic analysis generates large and complex datasets, we use chemometrics to elaborate the metabolomic fingerprinting thanks to its ability to provide interpretable models for complex inter-correlated data. By chemometrics, the measured metabolomic data produce important statistical control charts such as the multivariate statistical model PCA and even more the index dModX+, which are of great importance to classify products as good or poor quality products (Fig. 1).

Our study shows the results achieved on *grinTuss adulti syrup,* a natural complex product consisting of four main natural ingredients: honey, gumweed, curryplant and plantain fractions. We have identified and validated an analytical workflow that starting from an untargeted metabolomic fingerprint analysis and, using mass spectrometry and multivariate statistical analysis, can predict the quality of complex natural products (Fig. 2).

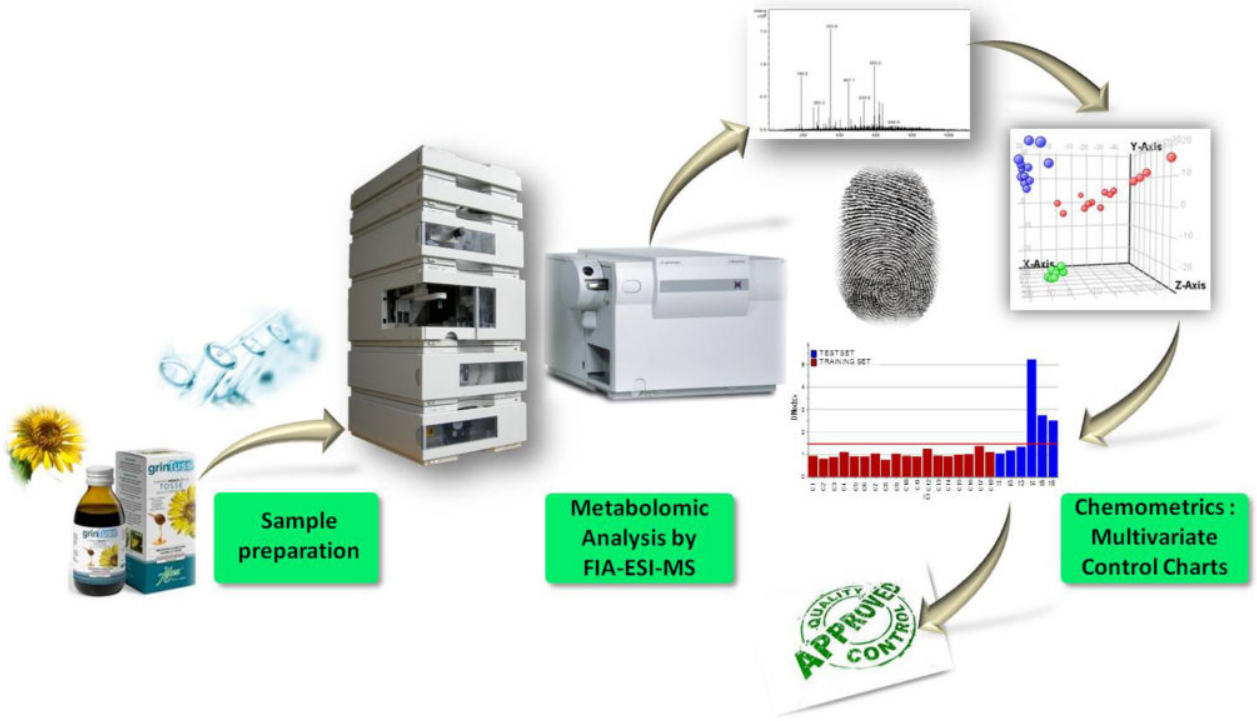

Fig. 2. Graphical abstract of the metabolomic analysis validated analytical workflow.

In conclusion, the conformity assessment of production batches using a metabolomic approach we proposed is new. Today technology is so friendly that we can make routine metabolomic analysis to perform quality control and the complexity of a natural product will no longer be a limit!

Luisa Mattoli
Ricerca Fitochimica, Aboca SpA Società Agricola, loc. Aboca 20, Sansepolcro (AR), Italy

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