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Editorial

Applications and Challenges for Metabolomics via Nuclear Magnetic Resonance Spectroscopy

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1. Introduction

Even though metabolomics is about 20 years old, the interest in this "-omic" science is still growing, and high expectations remain in the scientific community for new practical applications in biomedicine and in the agricultural field. Thus far, biomedical metabolomic studies have produced great advancements in biomarker discovery, identification of novel metabolites, and more detailed characterization of biological pathways involved in the manifestation and progression of diseases. In parallel, metabolomics has been shown to have an emerging role in monitoring the influence of different manufacturing procedures on food quality and food safety. In light of the above, this Special Issue was introduced to collect the latest research from various application fields of NMR-based metabolomics [1,2], ranging from biomedicine to data mining and food chemistry.

2. NMR-Based Metabolomics

Our collection comprises four research articles that report interesting applications of NMR metabolomics in the biomedical setting. In the first article published in our issue, Baranovicova et al. [3] present a longitudinal study that explores the dynamics of metabolomic changes in the plasma of 53 patients, diagnosed with SARS-CoV-2 infection, at three consecutive time points during their first week of hospitalization (days 1, 3, and 7 after admission to the hospital) to reveal the differences among patients with positive (survivors) and negative (worsening condition, non-survivors) outcomes. People with COVID-19, regardless their prognosis, presented alterations in their energy and amino acids metabolism. These changes were normalized by the seventh day in patients with positive outcomes; conversely, they were not reverted in patients with negative outcomes. These results indicate that the ability to respond to metabolomic alterations induced by severe inflammation due to SARS-CoV-2 infection is a key factor in determining patients' outcomes and that these metabolic changes can be tackled with individual pharmacological or diet interventions to support patient response.

In recent years, nanoscience and nanotechnology have been developing rapidly; at the same time, the increased use of nanoparticles has raised several concerns regarding human public health and occupational safety. In the article by Horník et al. [4], NMR-based metabolomics of exhaled breath condensate (EBC) and blood plasma is used to study the effects of occupational exposure to nanoparticles (NPs). The EBC and blood plasma samples from 20 workers exposed to NPs were collected pre-shift (i.e., before 2.5 h of exposure to NPs) and post-shift (i.e., after NP exposure). Moreover, 20 controls (not exposed to NPs) were enrolled for this study. Multivariate statistical analyses, performed both on EBC and plasma NMR data, showed clear discriminations among the three groups of interest (the pre-shift, post-shift, and control groups). The univariate metabolite analysis revealed several alterations in subjects exposed to NPs, in particular the acute effect of NP exposure is primarily reflected in the metabolic pathways involved in the production of

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antioxidants and of other protective species, whereas the chronic effect of NP exposure seems to be associated with alterations in glutamine and glutamate metabolism, and the purine metabolism pathways.

The paper authored by Vignoli et al. [5] characterizes the effects of surgery on the serum metabolomic profiles of colorectal cancer (CRC) patients and explores the possibility that metabolic variations among preoperative and postoperative serum samples could be informative on future cancer recurrence. A total of 41 patients diagnosed with early-stage CRC and scheduled for radical resection were enrolled for this study. Serum samples collected preoperatively (t0) and 4–6 weeks after surgery but before the start of any treatment (t1) were analyzed via ^{1}H NMR spectroscopy. A clear discrimination between t0 and t1 emerged: after surgery, there are significant increases in pyruvate, HDL cholesterol, HDL phospholipids, HDL Apo-A1, and HDL Apo-A2 levels, coupled with significant decreases in acetone, 3-hydroxybutyrate, LDL-Chol/HDL-Chol ratio, and Apo-A1/Apo-B100 ratio. Taken together, these results point to a relevant rearrangement of the metabolic pathways related to lipoproteins, ketone bodies, and energy metabolism. Furthermore, several differences between post- and pre-operative serum samples, in particular those related to the HDL-Chol and VLDL-Chol subfractions, seem to be associated with cancer recurrence. These data pave the way for novel strategies for risk stratification in patients with early-stage CRC.

The paper by Georgiopoulou et al. [6] is the last research article related to biomedical applications of NMR metabolomics included in our issue. It proposes an analysis of urine samples of preterm infants with neonatal sepsis, a systemic infection difficult to diagnose in its early stages and thus reporting high rates of morbidity and mortality. In this study, the urine metabolomic profiles of 34 septic neonates, 14 preterm neonates without sepsis or other serious morbidity but hospitalized in the NICU, and 23 healthy preterm neonates were examined. Multivariate and univariate statistical analyses showed clear discriminations between septic and healthy newborns. In particular, alterations in the levels of gluconate, myo-inositol, hippurate, taurine, N, N-Dimethylglycine, betaine, creatinine, glucose and lactose emerged as the most significant. These data represent a promising basis for future large-scale multicenter studies and give new perspectives for clinical research in the field of neonatology.

We decided to address also foodomics in our issue, which refers to metabolomic approaches applied to foodstuff for investigating topics related to nutrition, fraud detection and traceability of the geographical origin and production/processing procedures of food. In this regard, in our issue, we decided to publish an NMR-based metabolomic study based on water extracts of green and roasted coffee beans of different cultivars from three distinct Nicaraguan farms [7]. We think that this study can show well the potential and versatility of NMR metabolomics. Here, the authors demonstrate the potential of NMR metabolomics not only to define the geographical origin and the farm of provenance but also to characterize the effect of the environment (microclimates, irrigation, fertilizers, etc.) and the post-harvest practices (e.g., drying and fermentation) that are responsible for different aroma precursors in coffee and thus affect its distinct taste.

The ensemble of these studies offers a representative overview of the applications of NMR metabolomics raging from the biomedical fields to food science.

The capabilities of NMR, coupled with an ever-growing list of statistical chemometric techniques, make NMR-based metabolomics a versatile technique. Applying correct and suitable statistical techniques has become of fundamental importance for metabolomics studies. For this reason the review of Corsaro et al. [8], which lists some of the most commonly used and useful statistical techniques in metabolomics, explaining their advantages and disadvantages, has been included in our issue. In this work, the authors give an overview of the wide range of statistical opportunities for NMR-based metabolomics, ranging from conventional approaches (e.g., unsupervised and supervised methods, and pathway analyses) to less frequently applied deep learning and artificial neural networks. We found this review beneficial not only for fledgling metabolomic students approaching chemometrics but also for experts in the field looking for a more suitable approach to their studies.

In conclusion, the current Special Issue of *Applied Sciences* offers a variety of examples on how NMR-based metabolomics can potentially be used in several and varied settings. Although this Special Issue has been closed, more in-depth research on this topic is expected in the years to come, and future research will no doubt continue to explore the possibility of translating metabolomics into real-life applications.

Conflicts of Interest: The authors declare no conflict of interest.

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