NMR-Based Metabolomics in Food Quality Assessment

Subjects: Food Science & Technology
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The ability of nuclear magnetic resonance spectroscopy (NMR) to extract chemical information from a complex mixture is invaluable and widely described in literature. Many applications of this technique in the foodomics field have highlighted how NMR could characterize food matrices, and it can be used all along its "life chain": from farm to fork and from fork to the digestion process.

Keywords: nuclear magnetic resonance ; bioactive compounds ; food analysis ; food quality ; foodomics

1. Introduction

Food quality, food authenticity, and food safety are the most valuable targets to ensure and guarantee the needs of a world population that is increasing higher and higher. Consumers ask for much more security and, at the same time, for better information on food chemical and nutritional composition, origin, authenticity, and the effect of technological transformation on both the food's molecular profile and human health [1]. Furthermore, the bioavailability and bioaccessibility of the nutrients and/or bioactive compounds (BC), and the prediction of nutrition efficiency are additional key concepts in which consumers begin to be interested in [2]. They also become more sensitive to the environmental aspect, considering the deep global warming alarm in 2022, one of the warmest years since 2005 [3]. Nowadays, the attention on "what we eat" reflects not only the food's nutritional-health aspects but also "avoiding derivatization and favoring substances based on renewable sources" [4] by respecting the environment. In light of these global warming events, academics together with industry must work to ensure consumers' requests and to improve their human life. These pathways go hand-hand with sustainable development inevitably.

Thus, how can academics answer to the consumers' needs while being at the same time environmentally friendly? Secondly, how can NMR-based metabolomics play a key role in this scenario?

Before answering these two questions it is important to keep in mind the meaning of the word sustainable when we take into account academic research and, thus, analytical techniques. Płotka-Wasylka, et al. [5] defined sustainable as those analytical techniques that take into consideration three fundamental pillars: (1) the environment, (2) the economy, and (3) the society (**Figure 1**).

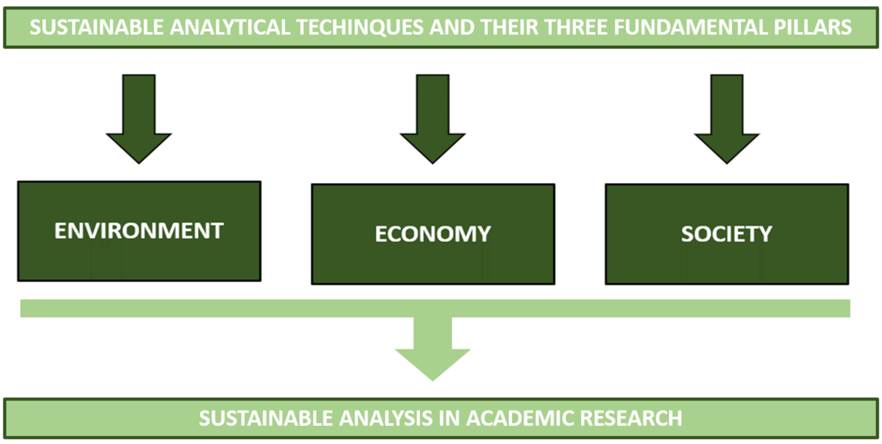

Figure 1. Sustainable analysis in academic research starts from sustainable analytical techniques that have to take into consideration three fundamental pillars: environment, economy, and society.

Pillar 1: Sustainability can be achieved by waste minimization, adopting green solvents, or focusing on solventless methods, energy savings, and trying to avoid the use of auxiliary reagents and chemicals [5]. Sustainable analytical techniques should also be considered to limit pollution.

Pillar 2: Academic research is generally recognized as curiosity-driven. However, there has recently been a shift in this, which was also influenced by the types of funding available. Research has become more industry-oriented and practical than conceptual. It has also started to suggest green solutions to problems and have an economic impact. Therefore, in the current context, food analysis and quality evaluation need to be supported by procedures and analytical techniques whose challenge is to reduce the environmental footprint [5].

Pillar 3: The main educational task is to transmit a clear message to society that would shed light on chemistry as a fundamental part of the solution to pollution problems and not just part of the problem. Information on the possibility of "making science" with low environmental impact is a fundamental leitmotif that society should have clearly in mind.

In the context of analytical chemistry, as well as in food analytical chemistry, some well-established methods require hazardous chemicals and/or a high energy demand for sample preservation, pretreatment, calibration, and analyte determination. Frequently, the analytical methods yield large amounts of waste with even higher toxicity than the target analytes. Thus, analytical chemistry plays an important role in the sustainable development of the planet [5]. For this reason, green chemistry (GC) is considered an important tool for achieving sustainability since it aims at the development of chemicals and chemical processes to reduce the impact on human health and the environment. But how can it be achieved? Poliakoff, et al. [6] suggest a deep change in attitudes and behavior in the chemical industry all along the chemical supply chain. For example, at the start of the chain, laboratories, where research is carried out, should be rethought and built to minimize the use of energy. At the other end of the chain, wherever possible, the amount of chemical(s) used to achieve a given effect should be decreased by a factor of two every five years [6], according to Moore's Law for Chemistry (MLFC) [7]. In this scenario, scientists are thus encouraged to develop or adopt new green analytical methods that (1) contribute to the reduction of pollution, including real-time analysis of pollutants; (2) avoid sample pretreatment or involve greener approaches for sample pretreatment, including safe solvents and auxiliaries; (3) use miniaturization and automation, including flow analysis and microfluidics and (4) use green separation techniques.

Based on these aspects, it is now possible to answer the second question: how can NMR-based metabolomics play a key role in this scenario? The High Resolution (HR)-NMR is a successful and functional research technology because of both its peculiarities which are listed in pillar 1 above. HR-NMR spectroscopy is one of the main analytical technologies that operates following the green chemistry guidelines in sample preparation [8]. Mielko, et al. [9] recognized the NMR as a green method as it requires for metabolomics studies only 10% D_2O (deuterated water) in 90% of distilled water (H_2O^{dd}). The solution has the characteristic of being versatile as it can be used in different studies. For example, this aqueous solution has been adopted for urine and serum fluid analysis, as shown by Trimigno, et al. [10] and Münger, et al. [11]. The authors used simply a phosphate-buffered saline (PBS) which also includes sodium azide (NaN_3) as an antibacterial agent and a 20 mM 2-chloropyrimidine-5-carboxylic acid (2CLPYR5CA) as the reference standard. Also, in the case of food metabolomics analysis, the NMR spectroscopic method requires simplicity in the analysis of polar metabolites. Their extraction can be performed by using a solution of trichloroacetic acid (TCA) 7% including 10% D_2O [12][13]. This application has been described in the work of Ciampa, et al. [14], where the authors show how the NMR satisfies, for the quantification of trimethylamine (TMA) content in fish, all the validation requirements at the same level as the most frequently used methods (as HPLC). Furthermore, the technique has the advantage of being faster and more repeatable, avoiding the use of solvents, such as toluene and formaldehyde, or dangerous reagents, such as picric acid.

2. The NMR-Based Metabolomics in Food Science and the Foodomics Approach

It is important, before exploring the potentiality of the NMR in metabolomics studies, to clarify what metabolomics studies are. The term "metabolomics" was introduced by Oliver Fiehn and defined as a comprehensive and quantitative analysis of all metabolites in a system [15]. On the other hand, the term "metabonomics" was coined by J. K. Nicholson in 1999 [16], and it represents "the quantitative measurement of the dynamic multiparametric metabolic response of living systems to pathophysiological stimuli or genetic modification." Nowadays, modern metabolic phenotyping (metabotyping) is known as metabolomics, encompassing both the comprehensive analysis of the small molecule content of the tested samples, and the changes that occur in response to a stimulus of one sort or another (physiological, pharmacological, or toxicological) [17].

The given definition points out the importance of the HR-NMR in "the augmentation and complementation of the information provided by measuring the genetic and proteomic responses to xenobiotic exposure" as it is appropriate "for investigating abnormal body fluid compositions", as a wide range of metabolites can be quantified simultaneously with no sample preparation and "without prejudice" [16].

In this light, Nicholson describes de facto the NMR-based metabolomics approach. In summary, it represents a high-performance fingerprinting process that examines the entire collection of small molecules (typically <1800 Dalton) that are present in a concentration above 10 µM, including sugars, amino acids, organic acids, and lipids, and is called 'metabolome' [18]. In summary, metabolomics is the final step of a more structured pipeline that involves more omics platforms, such as proteomics, transcriptomics, and genomics [15], as represented in **Figure 2**.

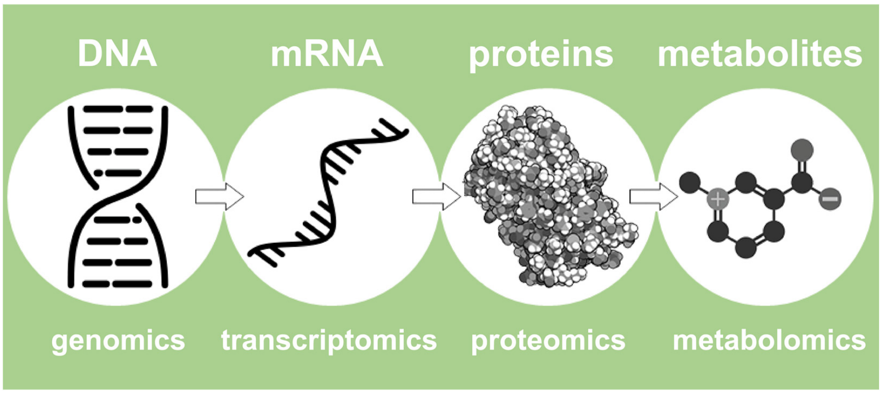

Figure 2. An outline of the four most important omics fields, ranging from genomics to metabolomics.

This integrated "snapshot" may change throughout the exposure to external factors or during organism development. When dealing with this technique, almost two kinds of approaches can be used for the analysis of the metabolome: (i) the target analysis, which is metabolic profiling, and (ii) pattern analysis, which is metabolic and metabonomic fingerprinting.

Target analysis, or metabolic profiling, is the identification and quantification of given and predefined metabolites [19]. It can be a specific metabolite or a selected number of metabolites. In the first case, a selective extraction is necessary before the NMR analysis to concentrate the selected metabolite. The latter case is used when the attention is focused on the specific role of a selected metabolic pathway; this approach is called metabolic profiling [20]. The pattern analysis is metabolic profiling obtained by identifying and quantifying all metabolites. This operation is led by using specific software, such as Chenomx [21][22], and it is called 'metabonomics.' On the other hand, metabolic profiling is used when sample classification without quantification of individual-specific metabolites is required [20]. In this case, the NMR spectrum becomes a fingerprint of the product, and all the NMR resonances/signals are measured without any identification [23], and it is called 'fingerprinting'.

Due to the above-all-mentioned characteristics, it appears clear why in the last 15 years academic researchers have employed NMR-based metabolomics in food science more and more. With this technology, academics meet the consumers' requests in one shot: a green approach that both pays attention to the environment in sample preparation and can assess and guarantee the quality of foodstuff. It is not a coincidence that with the opening of the food markets at a worldwide level, the number of research papers on the evaluation of food quality by using an NMR-metabolomics approach increased. Consonni and Cagliani [24] explain that the globalization phenomenon changes the definition of food quality that have to include also other aspects like geographical origin, sophisticated frauds, and adulteration practices, etc. The expansion of the food quality concept is also determined nowadays by the introduction on the market of new foods formulated to be much more sustainable and green [25]. These innovative foods are designed considering unconventional sources of nutrients, such as insects [26][27][28], for example, but also converting waste products into second-life products [29][30][31]. For this reason, consumers have to be reassured about food safety and from a nutritional value point of view. As these new aspects overcome the official analytical determination focused on specific compounds investigation, the role of metabolomics in this new quality assessment has become very important [24]. The importance is proved by the tremendous number of papers dealing with metabolomics and NMR that appear in the bibliography. Among them, geographical origin plays a key role as food quality is strongly affected by the particular conditions of production areas, which give unrepeatable organoleptic and nutritional properties to agricultural food products [32]. Extensive studies have been performed on several different foods to find out biomarkers able to classify them concerning their geographic origin: extra virgin olive oil (EVOO) [33][34][35][36], cheese [37][38][39], tomato [40][41][42], saffron [43][44], fruits and vegetables [45][46][47][48][49], honey [50][51][52][53] and wine [54][55][56][57][58], etc. Food frauds and adulteration have been largely taken in consideration in NMR-based metabolomics studies as well [59][60][61][62][63][64][65][66][67][68]. The application of NMR-based metabolomics in a food quality context can be included in the so-called foodomics, and we can talk about NMR-based foodomics. The first definition of this omics approach appeared in 2009 by Cifuentes [69], and it put attention on the investigation of all the possible connections among food, diet, and the individual, including health and ill impact [70]. These connections are included in the suffix "omics", which comes from the Latin word "omne" and it means everything, totality, wholeness, and entirety [71]. A more holistic definition by Cifuentes [72] described foodomics as "the discipline that studies the food and nutrition domains through the application and integration of advanced omics technologies to improve consumer's well-being, health, and confidence". This new approach then had much more resonance during the first International Conference on Foodomics, held in Cesena in 2009, where scientists were invited to contribute to the holistic definition of food in a multidisciplinary environment [73]. The academics' contribution to this new discipline is largely demonstrated by several papers describing in proper matter the aim and the applications of foodomics [71][74][75][76][77][78].

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