

Review

# NMR-Based Metabolomics for a More Holistic and Sustainable Research in Food Quality Assessment: A Narrative Review

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**Abstract:** 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. The aim of this review is an attempt to show, firstly, the potential of NMR as a method based on green chemistry in sample preparation, and then in characterizing the nutritional qualities of agri-food products (with particular attention to their by-products) from a sustainable point of view. For instance, the NMR-based metabolomics approach has been used to enhance the nutritional properties of bio-products waste naturally rich in antioxidants and prebiotics. The reintroduction of these products in the food supply chain as functional foods or ingredients answers and satisfies the consumer demand for more food with high nutritional quality and more respect for the environment.

**Keywords:** bioactive compounds; food analysis; food quality; foodomics; green analytical method; green sample preparation; in vitro digestion; metabolomics; nuclear magnetic resonance



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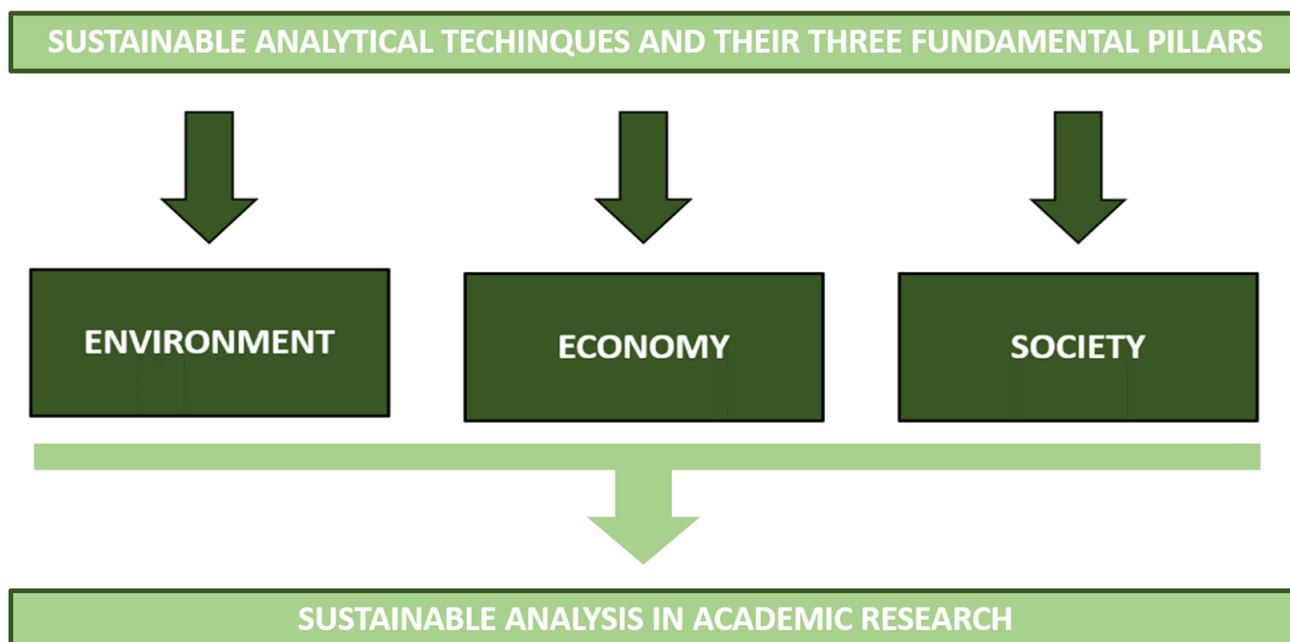
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## 1. Introduction

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-in-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-Wasyłka, 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<sub>2</sub>O (deuterated water) in 90% of distilled water (H<sub>2</sub>O<sup>dd</sup>). 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<sub>3</sub>) 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<sub>2</sub>O [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.

In addition to the lower environmental impacts in sample preparations, other peculiar characteristics make NMR spectroscopic methods very attractive for metabolomics analysis. Several papers highlight its capability to offer qualitative, as well as quantitative, knowledge about complex biological samples [15] and their high reproducibility. At the same level the NMR weaknesses, such as limited sensitivity and resolution of the spectra, are largely documented [9,16–18], and summarized in Table 1 in which we compared the two most important platforms used for metabolomics analysis, such as Mass Spectroscopy (MS) and NMR as well.

Anyhow, significant developments have been made to enhance the NMR sensitivity, including microprobes, cryogenically cooled probes [19], and the dynamic nuclear polarization (DNP) approach [20]. Another critical point about this technique regards the huge amounts of cryogens (helium and nitrogen) required that are impacting the environment quite deeply. The increasing growth of cryogen consumption and their limited resources are the challenges that industries will face in the future [21]. Anyhow, the present review is focused on the green aspect concerning NMR-based metabolomics samples' preparation so the cryogens matter has not been considered, even if their reduction is still a big deal.

**Table 1.** Key differences between NMR and MS as green tools for metabolomics research (adapted from Emwas [17]).

	NMR	MS	Is NMR ‘Greener’ than MS?
<b>Sensitivity and Selectivity</b>	Low sensitivity (can be improved using microfluidics, dynamic nuclear polarization, . . . ); Generally used for nonselective analysis	High sensitivity (nanomolar); Can be used for both selective (targeted) and nonselective (nontargeted) analyses	
<b>Sample measurement</b>	All metabolites that have NMR concentration level can be detected in one measurement	Usually needs different chromatography techniques for different classes of metabolites	
<b>Number of detectable metabolites</b>	40–200 depending on spectral resolution	≥300 (depending on MS techniques, whether GC-MS or LC-MS is used)	
<b>Reproducibility</b>	Very high	Moderate	
<b>Sample preparation</b>	Minimal	Complex (needs different columns and ionization methods)	
<b>Tissue extraction</b>	Not required (tissues can be analyzed directly using HRMAS NMR)	Yes, requires tissue extraction	
<b>Sample recovery</b>	Nondestructive; sample can be recovered and stored for a long time; several analyses can be carried out on the same sample	Destructive technique but need a small amount of sample	
<b>Sample analysis time</b>	Fast (the entire sample can be analyzed in one measurement)	Longer (requires different chromatography techniques depending on the metabolites analyzed)	
<b>Sample cost</b>	Low cost per sample	High cost per sample, more expensive than NMR	

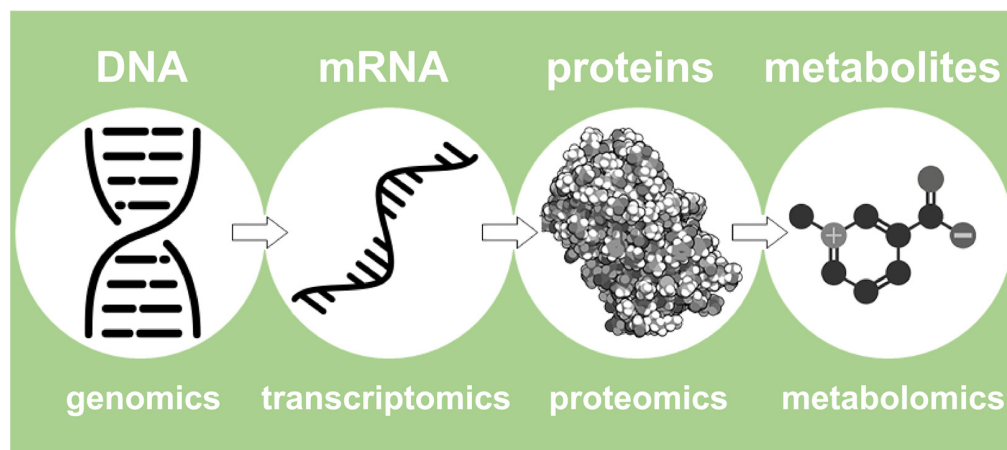
## 2. The NMR-Based Metabolomics in Food Science and the Foodomics Approach

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 [22]. On the other hand, the term “metabonomics” was coined by J. K. Nicholson in 1999 [23], 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) [24].

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” [23].

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  $\mu$ M, including sugars, amino acids, organic acids, and lipids, and is called ‘metabolome’ [25]. In summary, metabolomics is the final step of a more structured pipeline that involves more omics platforms, such as proteomics, transcriptomics, and genomics [22], 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 [26]. 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 [27]. The pattern analysis is metabolic profiling obtained by identifying and quantifying all metabolites. This operation is led by using specific software, such as Chenomx [28,29], and it is called ‘metabonomics.’ On the other hand, metabolic profiling is used when sample classification without quantification of individual-specific metabolites is required [27]. In this case, the NMR spectrum becomes a fingerprint of the product, and all the NMR resonances/signals are measured without any identification [30], and it is called ‘fingerprinting’. Due to the above-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 [31] 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 [32]. These innovative foods are designed considering unconventional sources of nutrients, such as insects [33–35], for example, but also converting waste products into second-life products [36–38]. 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 [31]. 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 [39]. 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) [40–43], cheese [44–46], tomato [47–49], saffron [50,51], fruits and vegetables [52–56], honey [57–60] and wine [61–65], etc. Food frauds and adulteration have been largely taken in consideration in NMR-based metabolomics studies as well [66–75]. 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 [76], and it put attention on the investigation of all the possible connections among food, diet, and the individual, including health and ill impact [16]. These connections are included in the suffix “omics”, which comes from the Latin word “omne” and it means everything, totality, wholeness, and entirety [77]. A more holistic definition by Cifuentes [78] 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 [79]. The academics’ contribution to this new discipline is largely demonstrated by several papers describing in proper matter the aim and the applications of foodomics [77,80–84].

### 2.1. The NMR-Based Foodomics Approach for Food Bio-Waste or By-Products Analysis

The valorization of the green aspects in the NMR-based foodomics leads to a green NMR-based foodomics approach [13], and it answers much more to the consumers’ “2.0” needs in terms of both food safety and quality, and sustainability. The green attribution has a twofold meaning: (1) green because, as it has been previously underlined, it involves “environment-friendly” chemicals (green chemistry). Castro-Puyana, et al. [85] demonstrate how foodomics can emerge as a green discipline by applying the basic concepts of Green Chemistry; (2) it is green because its challenge is to preserve sustainability, understood as a way of using and preserving what nature gives us in the most productive, environmentally safe way [85]. In the last years, foodomics started dealing with food ingredients able to improve our health, which means nutrients and BC. Thus, the extraction of BC from natural sources (such as plants, algae, food bio-waste, and food by-products, among others) and the quality analysis of functional foods (FF) is a key step in the foodomics workflow [16,85].

Food bio-waste or by-products from various sources can be fundamental for BC production and FF formulation. The high added value of these wastes is due to the content of BC, which, most of the time, is greater than in the edible part of the fruit [86]. For this reason, their proper waste management plays a vital role in the growth of food industries as they can contain valuable components such as polysaccharides, proteins, fats, fibers, and flavor compounds [87]. Azizan, et al. [88], by using <sup>1</sup>H NMR, described bioactive metabolites from pineapple waste. These compounds have antioxidant capacity and they can inhibit the activity of a carbohydrate-active enzyme ( $\alpha$ -glucosidase). In conclusion,

it emerges that 3-methylglutaric acid, threonine, valine, and  $\alpha$ -linolenic acid were the main contributors to the antioxidant activities, whereas epicatechin was responsible for the  $\alpha$ -glucosidase inhibitory activity. The metabolic composition of cherimoya leaves (*Annona cherimola* Mill.) is also characterized by the presence of BC, such as phenolic compounds. It is a deciduous tree from the Annonaceae family, typical of Peru and Ecuador, and its fruits are largely produced in Spain [86]. In this case, the metabolic composition has been profiled by using the  $^1\text{H}$  NMR coupled with high-performance liquid chromatography coupled with time-of-flight mass spectrometry (HPLC-TOF-MS). The first ( $^1\text{H}$  NMR) achieved 23 primary compounds, classified as amino acids, organic acids, carbohydrates, choline, phenolic acid derivatives, and flavonoids. The second (HPLC-TOF-MS) profiled 66 secondary metabolites among carbohydrates, amino acids, phenolic acids and derivatives, flavonoids, phenylpropanoids, and other polar compounds [86]. Similar antioxidant properties have also been identified in pistachio's hard shells [89], blackcurrant skin [90], olive oil by-products [36,37], and date palm by-products [91]. In this last case, a strong antioxidant activity has also been attributed to date fruits, whose bioactive metabolites have been profiled by  $^1\text{H}$  NMR by Kadum, et al. [92]. In this work, five different cultivars have been compared to find the one with the most antioxidant activity. The obtained results demonstrated that the extract from the Piyarom variety had both the highest total phenolic and flavonoid content and exhibited good antioxidant activity. The metabolites responsible for the antioxidant activity, glucose, ascorbic acid, epicatechin, gallic acid, and citric acid, were successfully identified using  $^1\text{H}$  NMR-based metabolomics [92].

Among the BC, a particular interest is covered by prebiotics which are defined as "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health" [93,94]. To guarantee their bioactivity, prebiotics have to (i) be resistant to gastric acidity; (ii) avoid absorption in the gastrointestinal tract; (iii) not be subjected to enzymatic activity; (iv) be fermented by intestinal microflora to produce short-chain fatty acids, and (v) be a selective substrate for the growth of intestinal bacteria associated to human health and well-being [95,96]. The main prebiotic agents consist of nondigestible carbohydrates, such as polysaccharides (POS), oligosaccharides (OS), and soluble dietary fibers (mainly inulin) [96]. Prebiotic foods are largely requested on the market; thus, food industries are working on the development of sustainable bioprocesses that can guarantee OS from a waste of different sources [97–99]. An important resource of OS comes from lignocellulosic agricultural waste disposals. Apart from bioethanol generation, several studies demonstrated the conversion of lignocellulosic biomass into oligosaccharides, through both microbial fermentation and enzymatic hydrolysis, by microorganisms or enzymes [100,101]. Jana and Kango [100], through enzymatic hydrolysis, produced Manno oligosaccharides (MOS) from agricultural waste and their structural aspects were assessed using both  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy. MOS respect all the important criteria of being a prebiotic as they are (i) gastrointestinal resistant, (ii) an active substrate promoting the growth of healthy bacteria, and (iii) able to confer antineoplastic properties without any cytotoxicity to normal cells [100]. The capability of prebiotics to enhance the growth of healthy bacteria can be exploited for the production of important physiological metabolites. An example is given by recent research from Hussin, et al. [102]. The study investigated the effect of different commercial prebiotics on enhancing natural gamma-aminobutyric acid (GABA) production in cultured yogurt. In addition, the metabolomics profile of the fermentation-derived biomolecules in yogurt has been obtained via NMR-based metabolomics. This approach was useful for comparing the major metabolite profile of freeze-dried GABA-rich yogurt (GY) and standard freeze-dried yogurt (SY). A total of 16 and 13 compounds were detected in GY and SY, respectively, and this difference may be due to the strain-specific metabolic activities of GABA [102]. According to pillar 1, described in the introduction, the choice of extraction methods to obtain any kind of BC is fundamental. Ethanol is an example of a green and sustainable bio-solvent as it is completely biodegradable and obtained by the fermentation of sugar-rich materials [103–105]. Also, dimethyl ether (DME), having a high

cetane number and favorable carbon/oxygen ratio, emerged in the spotlight as a cleaner, environmentally friendly, and high-efficiency ignition fuel [106]. Thus, green solvents are among the preferred ones for extraction processes. For example, Cerulli, et al. [107], compared several ethanol-based solutions to find out the best one for the extraction of primary metabolites and inulin from “Carciofo di Paestum” (*C. cardunculus* subsp. *scolymus*) PGI heads. For the first time, a comprehensive investigation of green extracts was performed by LC-MS and NMR analysis to highlight the occurrence of both specialized and primary metabolites, respectively. Among all the extracts, hydroalcoholic, infusion, and decoction extracts were the most interesting, showing higher peaks for flavonoids, quinic acid derivatives, and inulin than MeOH extract [107]. Inulin is a polymer found widely distributed in nature as a plant storage carbohydrate with a high value in human nutrition. It has prebiotic properties for its resistance to digestion in the small intestine, it can be fermented by colonic microflora, and it can stimulate the proliferation of commensal bacteria [107]. Hence, artichokes are a source of prebiotic dietary fibers but also a source of metabolites with antioxidant activity associated with their high phenolic content [108].

## 2.2. The NMR-Based Foodomics Approach for the Simulated Digestion and Absorption of Food

Food is a biological matrix where different food components are organized in a complex structure and interact with each other. The digestion process is needed to break the structure to release nutrients and other BC. Thus, the overall nutritional value of food and bioactivity of its components relies on the bioavailability, not only on the amount of both nutrients and BC [109]. Their bioavailability depends on several factors, including their bioaccessibility, which means the amount that can be released from the matrix during digestion and pass into the soluble fraction, becoming available for absorption. The composition of the food matrix and the processing which foods are subjected can influence digestion and, in turn, the bioaccessibility of its components. From this point of view, the evaluation of the *in vitro* digestibility of different food matrices subjected to different types of processing or transformation, for example, enriched with BC from by-products, represents a fundamental parameter for the determination of the nutritional value of foods, and the possible effect of nutrients and BC [110–113]. NMR-based metabolomics showed a fundamental role in the determination of both the bioavailability and bioaccessibility of BC in natural or enriched foods during simulated digestion and absorption.

The application of NMR methodology in this field respects the aim described in pillar 1: both the *in vitro* digestion and NMR analysis follow the green chemistry guidelines in sample preparation [109]. For the NMR, samples taken during digestion are prepared by adding to 1 mL of each sample, 160  $\mu$ L of 1 M phosphate buffer in deuterium oxide (D<sub>2</sub>O), containing 10 mM 3-TSP as internal standard. According to the evaluation of the bioaccessibility of BC, a work by Marcolini, et al. [114] demonstrated how it depends on several conditions, such as (1) digestion conditions (pH, enzyme concentration, and activity), (2) compound stability, and (3) interactions with other food components, as well as the supramolecular organization of the food molecules [115]. In particular, the work focused on the effect of pH on the solubility and bioaccessibility of carnosine obtained by the digestion of bresaola, a typical beef-based product of northern Italy (Valtellina) [114]. Carnosine is a water-soluble dipeptide with functional and biological properties, especially as an antioxidant [116].

The dependence of BC bioaccessibility and bioavailability from the supramolecular organization of molecules in food, in summary, the food matrix, is also well described by Fonteles, et al. [117]. The research paper described the effect of inulin on the bioaccessibility and bioavailability of BC naturally present in acerola juice by applying both *in vitro* digestion and NMR protocols. After inulin addition, the prebiotic juice and a non-prebiotic one were first treated by two different thermal processes and then subjected to *in vitro* digestion to evaluate the bioactive juice compounds' bioaccessibility and the juice composition. Inulin, beyond its prebiotic properties, also has a protective effect in preserving the organic



compounds after industrial processes such as thermal processing, and also improving the bioaccessibility of BC in the treated juice [117].

The combination of in vitro digestion and <sup>1</sup>H NMR has also been developed and employed in a work by Vidal, et al. [118], where the first aim of the paper was the study of the hydrophilic metabolites of raw and cooked sea bass (*Dicentrarchus labrax*) through NMR. First of all, the spectrometry technique has been used for both metabolites' identification and quantification, as well as to evaluate the effect of microwave cooking on them. The interest in this study was great because the results provided information concerning the presence and concentration of BCs among the hydrophilic metabolites of raw and cooked sea bass, and because it enabled monitoring of the advance of the proteolysis and of the release of hydrophilic metabolites at different points of the in vitro digestion of cooked sea bass fillets. Other interesting works based on <sup>1</sup>H NMR spectral data to study qualitatively and quantitatively the hydrolysis level in complex lipid mixtures, such as fish samples, have been published by Nieva-Echevarría, et al. [119,120].

### 3. Conclusions

Different applications in food assessment, from quality to digestibility, can be successfully addressed by the application of the <sup>1</sup>H NMR-based metabolomics together with approaches such as in vitro digestion. Along with the power of the NMR technique, its attention to sustainability and low environmental impact in sample preparation were also emphasized. The green (NMR-based metabolomics) foodomics makes a valuable contribution to metabolites' profiling of complex samples, such as foods and food by-products. Bioactive compounds like prebiotics or antioxidant metabolites can easily extract from these products by following and respecting the green chemistry protocols, for example, by using water/ethanol solutions. The applications of this approach are not limited to what has been described as food metabolomics, but several works in the nutritional field have been reported in the literature, and it goes under the name of "nutri-metabonomics". This new "omics" approach can be considered the foodomics for healthy nutrition, and it offers valid tools to investigate the effect of nutrients or specific dietary components (BC, for example) on the human metabolome and metabolic regulation [121,122]. Therefore, it is clear that the NMR approach can meet the consumers' needs in an environmentally friendly way while also being a good method to detect food quality parameters. The next step to make NMR much greener towards the environment's needs is also to limit the use of cryogenics liquids which are a serious problem considering their scarcity.

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