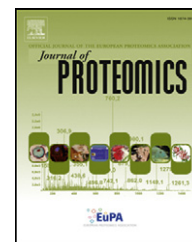


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Review

Biomarker discovery and applications for foods and beverages: Proteomics to nanoproteomics [☆]

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ABSTRACT

Foods and beverages have been at the heart of our society for centuries, sustaining humankind — health, life, and the pleasures that go with it. The more we grow and develop as a civilization, the more we feel the need to know about the food we eat and beverages we drink. Moreover, with an ever increasing demand for food due to the growing human population food security remains a major concern. Food safety is another growing concern as the consumers prefer varied foods and beverages that are not only traded nationally but also globally. The 21st century science and technology is at a new high, especially in the field of biological sciences. The availability of genome sequences and associated high-throughput sensitive technologies means that foods are being analyzed at various levels. For example and in particular, high-throughput omics approaches are being applied to develop suitable biomarkers for foods and beverages and their applications in addressing quality, technology, authenticity, and safety issues. Proteomics are one of those technologies that are increasingly being utilized to profile expressed proteins in different foods and beverages. Acquired knowledge and protein information have now been translated to address safety of foods and beverages. Very recently, the power of proteomic technology has been integrated with another highly sensitive and miniaturized technology called nanotechnology,

Abbreviations: CFU, colony forming unit; CLA, conjugated linoleic acid; CPLL, combinatorial peptide ligand library; DLDI, direct laser desorption ionization mass spectroscopy; GEPIs, genetically engineered proteins for inorganics; HPLC, high-performance liquid chromatography; MALDI-MS, matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry; MS/MS, tandem mass spectrometry; PBMCs, peripheral blood mononuclear cells; PCA, principal component analysis; PR, polyphenol rich; ROS, reactive oxygen species; SAW, surface acoustic wave; SERS, surface enhanced Raman spectroscopy; SPR, surface plasmon resonance; 2-DGE, two-dimensional gel electrophoresis; QCM, quartz crystal microbalance.

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yielding a new term nanoproteomics. Nanoproteomics offer a real-time multiplexed analysis performed in a miniaturized assay, with low-sample consumption and high sensitivity. To name a few, nanomaterials – quantum dots, gold nanoparticles, carbon nanotubes, and nanowires – have demonstrated potential to overcome the challenges of sensitivity faced by proteomics for biomarker detection, discovery, and application. In this review, we will discuss the importance of biomarker discovery and applications for foods and beverages, the contribution of proteomic technology in this process, and a shift towards nanoproteomics to suitably address associated issues.

This article is part of a Special Issue entitled: Translational plant proteomics.

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1. Introduction

The combination of various omics technologies, system biology, applied to specific nutrients or other dietary factors will greatly facilitate the discovery of new biomarkers. A recent discipline that has emerged applying the advanced omics technologies to human health and well-being is ‘foodomics’ [1]. The field is directed towards preventing future diseases through adequate food intakes, nutraceuticals, and functional foods [2]. Indeed, foodomics is a multi-faceted approach that tackles the biological complexity of the sample under investigation from several perspectives: from the genome (nutrigenomics) to the transcriptome (nutritranscriptomics), proteome (nutriproteomics), and metabolome (nutraceuticals), followed by introduction of a mathematical and statistical modeling in order to interpret biological phenomena in light of high-throughput results (nutranteractomics) [3] (Fig. 1).

Nutrigenomics builds the scientific foundation for understanding the variability in diet preferences, nutritional requirements, and responses to a certain diet among different humans and human populations. It may become the future tools for consumer assessment motivated by personalized nutritional counseling for health maintenance and disease prevention. Nutriproteomics plays a central role in nutrigenomics, which attempts to holistically understand how a genome may differentially be expressed as a response to one diet to another. From a molecular perspective, nutritional proteomics allow to discover

and quantify biomarkers and bioactives with proteins being the key actors in virtually all biological processes in the human body. Finally, metabolomics represents one founding pillar of foodomics [4,5] since metabolism is often considered to be ‘one-step closer to the phenotype’ in comparison to the other omics, in that protein expression is not necessarily tied to enzymatic activity, owing to the tuning effect of posttranslational modifications (PTMs) and, above all, phosphorylation [6]. Clearly, holistic and integrative approaches are therefore primordial.

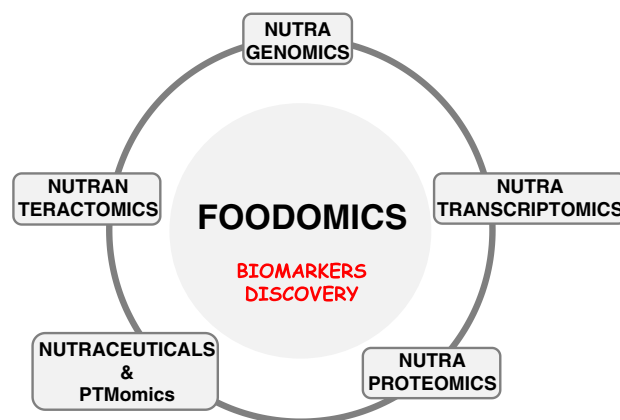


Fig. 1 – The clash of the “foodomics” — a system-oriented biology.

Food-derived proteins and peptides provide much more than basic macronutrients and building blocks for protein turnover. Bioactive proteins and peptides are a large and significant class of nutraceuticals that can be isolated, purified, and characterized by several proteomic tools. A nutraceutical is a bioactive food component that can add value to a food and cause the prevention or treatment of diseases. An essential part of food consists of macronutrients (carbohydrates, proteins and peptides, lipids) and micronutrients (such as vitamins and minerals). Biologically active motifs in the polypeptide chains of proteins are defined as fragments that remain inactive when inserted in the sequences of their own precursors, whereas upon release by proteolytic enzymes, they may interact with appropriate receptors, thus exerting specific bioactivity. The activity of such peptides may be either favorable or detrimental [7]. The beneficial attributes of bioactives range from anti-oxidant, anti-microbial, and anti-hypertensive agents to modifiers and regulators, in intracellular and extracellular signaling pathways. Thus, the characterization and quantification of such bioactive ingredients in food as well as their bioavailability and bio-efficacy once processed in the human gut are of interest, especially for personalized nutrition.

Besides bioactive proteins and peptides, a biomarker is a measurable change related to a phenotype. Molecular biomarkers are, for example, a variation in mRNA, protein, or metabolite concentration, and these should be responsive, specific, and applicable. Biomarkers help understand nutrient absorption, transport, and metabolism within an organism to produce an effective dose at target tissue. Biomarkers of susceptibility consider host, environmental and lifestyle factors, and in particular genetic predisposition. A valid nutritional biomarker can also function as a key measure linking a specific exposure of a dietary compound to a health outcome and thus offers great potential to understand the relationship between diet and health. However, given the complex interplay between nutrition, other environmental factors, and inter-individual variability on the host side, biomarkers alone will not explain the relationship between diet and health. In any case, biomarkers are indicators of molecular and cellular events in biological systems and help epidemiologists and clinicians better understand relationships between food constituents, whole food or diets, and human health effects.

Biomarker development and measurement highly depend on appropriate analytical tools to identify and quantify often minute amounts of bioactive compounds in food or biological specimens, and to monitor molecular changes in the body in a highly specific and sensitive manner. Thus, the identification of biomarkers as well as bioactives represents the ultimate tool for the improvement of early diagnostics, patient monitoring and for the evaluation of the safety and efficacy of therapeutic strategies [8,9]. Unfortunately, biomarkers are present in a very low amount together with many other chemical substances. Hence, identification and characterization of extremely low-abundance metabolites are two of the most relevant applications of clinical proteomics. The detection of such low-abundance biomarkers in a given biological sample thus requires even faster and sensitive detection technologies. Consequently, the integration of proteomics and nanotechnology has led to the development of nanoproteomics, providing a robust, real-time analytical platform for sensitive detection of low-abundance proteins [10,11].

Regarding foodomics, foods and beverages are the only physical matter we take into our body, therefore their detailed nutripoteomics analysis can better allow to discover natural nutraceuticals and bioactive components present in our diet. In this context and as the title of this review goes, we will focus on proteomics and nanoproteomics of foods and beverages.

2. Proteomic-based discoveries in foods and beverages

2.1. Food proteomics

Food quality and safety, and their influence on the health of end consumers have increasingly become a founding principle in the international agenda of health organizations [12]. Over the last decade, proteomics have been successfully applied to the study of quality control in production processes of food (including meat, wine and beer, transgenic plants, and milk), and food safety (screening for food-derived pathogens) by exploratory analyses of food of various origins and beverages, and in parallel to the genomic and transcriptomic approaches seeking determination of quantitative trait loci.

Evidences have been shown for the health-promoting aspects of plant-based diets, such as Mediterranean cuisines, which are rich in important phytochemicals. Among them, peptides, isoflavones, globulin, fatty acids, and finally milk and meat are of particular importance as the most consumed foods. Some phytochemicals like lycopene in tomatoes, soy isoflavones, and flavonoids from fruits have demonstrated anti-cancerous benefits [13]. Though no single phytochemical demonstrates proven health benefits, a synergistic action of several phytochemicals can offer a protective action [14].

Peptides have been found in soybean with a capability to stop cancer cell division in a skin cancer mouse model, and also to inhibit core histone acetylation in mammalian cells [15]. Soy-based diets have been shown to promote a cardio-protective effect, which is attributed to soy isoflavones as well as soybean proteins. Beermann and colleagues, utilizing the Trolox-equivalent anti-oxidative capacity assay, characterized the anti-oxidative capacity of enzymatically-released peptides from soybean protein isolates, offering new nutritional applications as molecules with free radical scavenging properties and with capacity to prevent and treat oxidative stress-related diseases [16]. Fuchs and coworkers studied the effect of isoflavones and genistein, as the most abundant compounds in soy seeds, with regard to the protective activity against atherosclerosis, and found that genistein at both low and high concentrations reversed the stressor-induced decrease of anti-atherogenic proteins [17]. The same group also revealed that soy isoflavones increase anti-inflammatory activity in peripheral blood mononuclear cells (PBMCs) from postmenopausal women [18]. A total of 29 proteins were identified as biomarkers that showed significantly altered expression in PBMCs, including a variety of proteins involved in anti-inflammatory response [18].

Recently, a label-free high-performance liquid chromatography (HPLC)-chromatin immunoprecipitation (ChIP)-tandem mass spectrometry (MS/MS) method was applied to the characterization of storage proteins in seeds of different *Lupinus albus* cultivars [19]. About 90% of the lupin seed proteins are globulins

that act as storage proteins. Among them, β -conglutin and γ -conglutin are the most relevant to nutrition [19] for their bio-active properties. The β -conglutin is thought to be hypo-cholesterolemic, based on its high homology with the R subunit of α -conglycinin [20], which is the major bioactive of soy proteins [21]. By contrast, γ -conglutin has a hypo-glycemic effect.

Besides proteins, fatty acids (FAs) contained in fish dietary and vegetable oils also have significant effects. Proteomic analyses revealed two distinct atherogenic effects of two structurally identical isomers of conjugated linoleic acid (CLA): trans-10-cis-12 CLA and cis-9-trans-11 CLA [22]. The former showed pro-atherogenic effects and induced insulin resistance in ApoE^{-/-} mice, while the latter was anti-atherogenic and induced heat shock protein (HSP70) expression. A differential expression of long chain acyl-CoA thioester hydrolase (for β -oxidation of FAs in liver) and adipophilin (for hepatic lipid accumulation and triglyceride synthesis) was observed with intake of dietary fish oil, trans-10, cis-12 CLA, and the combination with olive oil [23]. Moreover, FAs from olive can lower risk of plaque formation but increase the risk of hepatic steatosis. In induced colorectal carcinogenesis, glycolysis and mitochondrial FA breakdown were altered by dietary quercetin [24].

Immune-relevant food sources (such as milk) have been extensively investigated by MS for their protein and peptide complements. A few nutritional interventions have been monitored vis-à-vis their immune effects, mainly assessing the PBMC proteome that serves as an accessible and relevant immune cell population readily amenable to MS-based proteomics. Incorporation rates of amino acids, liberated during digestion of labeled milk protein and incorporation into plasma proteins, were measured in humans [25]. Human milk and bovine milk are two of the richest physiological liquids, whose function has always been tied to the provision of nutrients to offspring [26]. In recent decades, milk has been more and more suggested to contribute to postnatal development of the newborn, through stimulation of their anatomical growth, maturation of their immune system, completion of their digestive tract, and the establishment of symbiotic microflora. Analytical studies have revealed qualitative and quantitative differences in milk composition for major proteins, lipids, and carbohydrates from various mammals [27]. On the other hand, comparative genomic and bioinformatic studies have suggested a general conservation of milk and mammary genes/proteins among mammalian species, proposing species-specific milk variations associated with gene duplication and transcriptional/translational regulative events [28,29].

As farm animals represent the most important source of proteins in Western countries, there is increased attention to the study of the protein fraction in meat [30]. Recently, focus is on the identification of suitable biomarkers as indicators of meat quality and, in particular, of meat tenderness. The observations of Laville and coworkers [31] through two-dimensional gel electrophoresis (2-DGE), on tender vs. tough meat from young Charolais bulls, resulted in the postulation of a role for apoptosis in the linkage between animal slaughter and meat physico-chemical properties. In that study, higher quantity of proteins of the inner and outer membranes of mitochondria was found in the tender group, suggesting a more extensive degradation of mitochondria likely to be related to the apoptotic process [31].

Accordingly, correlation analysis in Chianina and Maremmana cows [32] revealed significant correlations of three of the identified actin fragments and the myosin heavy chain fragment with shear force. Myosin light chain II and triose phosphate isomerase I were also found to correlate significantly with shear force.

Guillemin and coworkers pursued the identification of actual biomarkers related to meat tenderness [33], and reported the individuation of 24 likely proteins whose quantitation paralleled beef tenderness in relation to muscle and animal type. Analogously, Morzel and colleagues [34] pinpointed the small HSP27 as one of the main biomarker candidates for beef tenderness in the *longissimus thoracis* muscle of French Blonde d'Aquitaine bulls. This protein is known to play a role in mitochondrial apoptotic pathway and might be well related to the observations by Laville and coworkers [31], or rather be involved in the protection of down-stream proteins (structural proteins, such as actin; [35]) from protease- or reactive oxygen species (ROS)-induced fragmentation, due to its chaperone activity.

In the case of pigs, the individuation of pyruvate kinase M1 and tropomyosin levels in Large White were related to water-holding capacity and Minolta values at 24 h after slaughter. Conversely, enzymes taking part in branching glycolytic reactions, such as glycerol 3-phosphate and creatine kinase M, were related to accentuated lipogenesis and slower albeit prolonged glycolytic rate in Casertana, respectively [36]. Thus, breed-specific differences at the protein level were not only related to growth performances and fat accumulation tendency in vivo, but they also affected postmortem performances through a direct influence on the forcedly anaerobic behavior of pig muscles after slaughter [37].

Moreover, redox proteomics are linked to the study of meat quality, as protein oxidation appears to contribute significantly to the tenderness of the meat through triggering the formation of both protein fragments and aggregates [38]. In fact, oxidation of proteins may cause changes in protein hydrophobicity, conformation, and solubility, and alter susceptibility of protein substrates to proteolytic enzymes [39]. This has been regarded as a major cause for the low digestibility and hence, lesser nutritional value of oxidized proteins [40].

Finally, quality control is a fundamental principle in the alimentary industry when it comes to genetically-modified organisms. With the final aim to detect unintended effects in transgenic crops, profiling techniques (such as proteomics) have been tested in order to identify newly expressed or over-expressed proteins upon genetic engineering of the plant [41]. The proteomic profiles of one transgenic maize variety (event MON 810) were analyzed [42]. Forty-three proteins were up- or down-regulated in transgenic seeds with respect to their controls, which could be specifically related to the insertion of a single gene into a maize genome by particle bombardment [42].

2.2. Beverage proteomics

In recent years, significant results have been achieved for proteomics applied to beverages by using the combinatorial peptide ligand library (CPLI) technique, that has greatly accelerated the identification of low- to very low-abundance proteins in biological extracts (for reviews, see [43–45]). In fact,

in the specific case of alcohol-free aperitifs, only using a technique (CPLL) so sensitive would have revealed the presence of many proteins [46]. The species identified belong to alpine herbs and plants, living in a habitat at altitudes between 1000 and 2000 m of elevation, and this allows tracing the plants used for the production of aperitifs. They may have a number of pharmacological properties, in addition to their carminative, tonic, appetite stimulating and digestive effects, ranging from anthelmintic, anti-spasmodic, diuretic, anti-pyretic, analgesic, liver, stomach troubles to curing even hemorrhoids, cancer, vertigo, anemia, anorexia, and dysmenorrhea [47–49]. To the possibility of certifying the genuineness of such aperitifs, identifying the global proteome is important, especially for famous aperitifs that can be counterfeited. The same authors have applied the same method to determine the proteome of alcoholic beverages, such as cynar, a typical Italian liqueur made by artichoke, with the final aim not only to identify as many as possible proteins in artichoke leaves, but also for the detection of plant proteins in the Italian liqueur stated to be an infusion of such leaves [50]. The authors argue that the detection of vegetable proteins (if any) in this aperitifs could test the genuineness of this alcoholic drink, while additionally guaranteeing consumers' protection against adulteration and imitation products invading the market [51]. Again, Fasoli and colleagues, applying the proteominer to determine the proteome of the ginger beverage, concluded that customer's looking for the correct drink, not made with artificial chemicals but with genuine vegetable extracts, can look at the "proteomic signature" that will identify the correct origin of such beverages [46].

Much research has been done on the grapevine due to its economic importance, mainly related to the production of juices, liquors, and wines. In particular, considerable attention has been devoted to the study of the grapevine proteome, since proteins are responsible for the majority of biological transformations that affect the plant and fruit development: they are involved in the general metabolism, such as cell rescue and defense, production of important metabolites, and transduction of signals. However, one of the key points in the investigation of grapevine proteins is that they could survive vinification and cause serious damage to the final product [52]. Many works in the past were devoted to the analysis of the so-called haze proteins, and more recently proteomic approaches have been used to have a better understanding of their characteristics. In fact, the detailed knowledge of the protein content and characteristics of grape berries and juices is important for winemakers, since protein precipitation is a major cause of haze formation in wines, and especially in white wines [46,53,54]. The large number of publications on grape and wine protein profiling published over the last few years has highlighted numerous aspects. Nevertheless, proteins could also be considered as important constituents in wines, for example in the sparkling wine industry, because they promote foam formation and stability [55]. Recently, the elicitation effect of chitosan on the proteome of *Barbera* cell suspensions was studied by Ferri and colleagues [56]. Furthermore, grapevine is considered a source of health-promoting secondary metabolites [57,58], the most important being the antioxidant resveratrol [59]. Thus, from a scientific point of view, in addition to its economic role, grapevine is considered more and more as a

model plant, thanks to the efforts in grape genome sequencing [60,61]. Efforts are now required to characterize red wine proteins, with a special focus towards consumer safety and product quality. Some of the proteins detected in both wine and in grape berries, such as chitinase and lipid transfer protein, are known to be allergenic [62,63], and this may be a severe threat to its commercialization. In addition, some of the fining agents traditionally used in wine making are also allergenic (e.g. albumin and casein).

Beers contain gluten derived from grains used in the brewing process. The complete suite of hordeins in purified hordein preparations, wort and beer and relative quantification of the most abundant hordein (gluten) proteins has been performed by Colgrave and colleagues [64]. Of interest, a large number of the C-hordein fragments were observed in wort with only trace levels of C-hordein peptides detected in beer. The characterization of beer in the absence of enzymatic digestion clearly demonstrates that in addition to intact hordeins, a large number of partially degraded hordein fragments are present and these may also contribute to coeliac toxicity. Many of these peptide fragments contained repeats of glutamine and proline that may elicit an immunological response in coeliacs. Coeliac disease is exacerbated by the intake of prolamins present in wheat, rye, barley, and in some coeliacs, oats. The only treatment for coeliac disorders is a life-long gluten-free diet. Many food products have entered the market suitable for coeliac disease patients, who make up ~1% of the population.

A recent study by Mullen and coworkers [65] examined the effect of a polyphenol rich (PR) drink on biomarkers assessed by urinary proteomics. Investigations clearly emphasized the potential of urinary proteomic analysis in assessing potential effects of food supplements (especially polyphenols) on pathological processes. In fact, a large number of biomarkers for a range of diseases based on panels of urinary peptides and peptide profiles have been developed by this and other groups [65,66].

The beverage industry, now-a-days, claims the introduction of plant and fruit extracts in the formulation of certain food products for food authenticity [67]. Thus, in this case, the identification of protein specific to the fruit or plant extract that is claimed being used in the formulation is a way to assess the genuineness of the products. Unfortunately, evidence demonstrates that there is no single 'ideal' biomarker that can identify a specific disease at an early stage. However, by using a 'fingerprint' of a number of peptides it is possible to identify pre-symptomatic development of a range of diseases [67].

3. Potential biomarkers and their applications for food and beverage quality, technology, authenticity, and safety issues

Global organizations have demonstrated a role in transferring the research knowledge directly to the field applications [68,69]. Food science and technology is one of the fields that have benefited the most from the advances in current proteomic techniques. Proteomic platform allowed to translate scientific knowledge into discovery and quantification of biomarkers that can allow to assess predisposition, efficacy

and characterization, and quantification of food bioactives [67], useful for the solutions of problems in food quality, safety, and nutrition, and ultimately human health (Fig. 2).

Knowledge obtained from proteomics can be translated into direct problem solving for the postharvest industry of horticultural crops. The wine industry, for instance, has gained meaningful information from proteomic research and readily translated this into improvements of the process. Analysis of the postharvest withering process in grapes is a key for obtaining high quality wines. Ripening process of grape has a direct impact on wine quality [70], wine spoilage and thus quality can be tracked by gel-based proteomic means [71]. The first proteomic analysis of grape ripening was conducted by Deytieux and coworkers [72], who compared the proteome of grape skins over three ripening stages from the beginning of véraison (i.e., the stage of growth when the color changes) until full maturity. Interestingly, champagne wine's quality is associated with the foaming properties and loss of foaming properties is associated to the loss of proteins [73].

Understanding the ripening processes and postharvest physiology during storage (low temperature, modified atmosphere) has not only a direct impact on food quality but also on the optimization of the technological processes involved, given that a series of abiotic stresses is applied (low/high temperature, modified atmosphere). For example, a recent proteomic study on the application of heat treatment on peach fruit indicated that all the proteins identified as being differentially expressed were involved in the regulation of peach fruit development and ripening, implying that this treatment could be used to improve fruit quality and shelf-life [74]. Proteomics have been successfully used to identify protein markers to select suitable cultivars for flour [75]. Selection of appropriate durum wheat cultivar for pasta making [76] confirmed that flour quality is highly correlated with protein composition and functionality.

Besides wine, beer quality is strongly associated to barley cultivar and the level of protein modification during malting. Thus, barley proteome map proved useful for detection and potential manipulation of beer proteins related to quality [77]. Many other proteomic applications have been carried out for a better optimization of the technological processes [74,78].

However, there are excellent reviews that summarize biotic and abiotic stress proteomics and the readers are referred to those reviews [79,80].

Another interesting application regards methods to assess the geographical origin of products to prevent illegal adulteration. In fact, assessment of geographical origin is one of the main requirements for the certification of wine authenticity, grape variety, wine age, and technology for production and proteomics can provide the biomarkers for such purposes [81] as well as assessment of the floral origin of honey has been performed using protein markers [82].

Any prediction at the animal level performed by system biology would result in many practical applications, including the improvement of phenotypic traits, especially those with low heritability, among which there are meat quality traits [83]. Now-a-days, proteomics can be an actual tool readily adoptable in the field of meat quality assessment [84,85]. Proteomics, for example, have been exploited either to monitor small peptides from glycolytic proteins released during processing of dry cured ham [86], which could determine qualitative signatures of seasoning progress, or rather to investigate and determine the presence of protein mixes from different animal species in order to discover meat adulteration cases [87]. These examples represent clear demonstration of the rapid shift of proteomic knowledge in the field of meat science to actual applications in the quality control processes of the food production chain.

The translation of proteomic research in the field of food allergens is quite extensive [68] because development of sensitive detection/quantification methods is crucial for allergen diagnosis, therapy, and risk assessment and for reinforcing current legislation on the subject. To this regard, proteomics could be used throughout the food processing steps to track the history of allergens, adjust processing steps and even predict shelf life. Microbial proteomic knowledge can be incorporated and implemented for food and plant/facility sanitation and safety assessment [68].

3.1. Discovery of bioactive proteins and peptides derived from food

Recent advancements in the fields of biochemistry and molecular biology have seen the use of proteins as potential candidate biomarkers for quality testing in various endeavors [88,89]. The role of proteomics in the discovery of biomarkers in gastrointestinal diseases has been outlined by Song and Hanash, where guidelines for biomarker development are described [90]. In this view, proteomic research has been focused on the individuation of quality markers of various foods, from meat to vegetables, of biological or genetically engineered origin [91]. Once individuated, these long sought after protein quality biomarkers can be monitored throughout industrial production processes, in similar fashion to the actual application of proteomics in other fields of research [92,93]. The interested reader is referred to D'Alessandro and Zolla [30].

However, it is important to underline that in order to exert any activity a bioactive compound must reach the target organ at a minimal concentration that determines both biological effect and mechanism of action. Bioactive peptides may be released during the digestion by host enzymes like

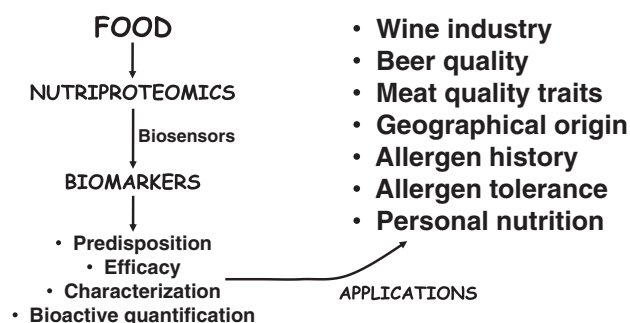


Fig. 2 – Biomarker discovery and applications. Nutriproteomics platform allows translating scientific knowledge into discovery and quantification of biomarkers and their applications for safety issues.

trypsin or by microbial enzymes (Fig. 3). For these reasons, in nutrition it is desirable to also generate information on absolute amounts of these peptides and proteins. This is because the basis of proven bioavailability and bioefficacy of a given ingredient lies in its absolute amounts in the original food matrix as well as in the relevant body fluids or tissues. Bioactive peptides and proteins have been reviewed by Moller and colleagues [7] and readers are referred to that for details. A database of bioactive peptides has also been developed for determination of potential bioactivity of food proteins and their classification [94]. In the near future, the identification of potentially active food constituents and the demonstration of their bioavailability and efficacy will lead to develop “functional foods” for specific diseases or personalized nutrition (see below). Biomarkers have been proven as being an important tool to understand the latter. Moreover, when combined with biomarkers of susceptibility [95], they should help to understand and explain the responsiveness of humans to dietary components, whole food or individual compounds, and ultimately reveal the relationship between nutrition and health.

However, bioactive peptides and proteins can also originate from food processing (industrial processing) or ripening (naturally occurring enzymatic reactions). In order to accurately address questions of bioavailability and bioefficacy, both systemically (i.e., in blood) and locally (e.g. in the gut), they must be identified and quantified all across from food matrix to the target tissues in the body. However, dietary intake of a bioactive compound does not necessarily reflect the dose reaching the target tissue.

According to present knowledge, bovine milk, cheese, and dairy products seem to be by far the richest sources of bioactive proteins and peptides derived from food. This may be due to the particular purposes to which milk is dedicated beyond nutrition in the first few months of life. On the other

hand, the individuation of the differential proteomic profiles of human milk and bovine milk could be exploited to ameliorate milk formulas for infants, thus guaranteeing products of improved quality while excluding the likelihood of insurgence of adverse immune reactions [96]. In fact, as milk represents the main source of nutrition for infants, the question of an effective human milk substitute becomes mandatory when a formula-fed baby is allergic to cow's milk proteins [97]. In this case, formulas containing extensively hydrolyzed milk proteins should be preferred, but even such a formula may cause allergic reactions in highly sensitive patients. If there is evidence of allergy to cow's milk with IgE-associated symptoms, after six months of age, a soybean formula may be recommended only when tolerance to soy protein has been established by clinical challenge. In infants with allergic reactions to cow's milk proteins, even after extensive hydrolyzation, proteomic techniques coupled with immunological methods may make it possible to select other milk products that do not contain the same allergens as ordinary cow's milk.

Although bovine milk and dairy products were originally the source for food-derived bioactive proteins and peptides, extensive research in this area has uncovered bioactive peptides from other animal and plant source cereals. In bovine blood, gelatin, meat, eggs, and various fish species such as tuna, sardine, herring, and salmon, as well as in wheat, maize, soy, rice, mushrooms, pumpkin, and Sorghum, bioactive proteins and peptides have been detected either directly or after release by hydrolysis or fermentation [7]. In cereals, such as rice, wheat, and barley; legumes such as soy; vegetables such as mushrooms and pumpkin; meat and sea foods [7] and through studies in cell cultures, animal models and clinical trials, their effects as anti-cancer, anti-hypertensive, anti-diabetic, anti-obesity, immune-modulatory, hypo-cholesterolemic, opioid, and anti-oxidant agents have been demonstrated [98,99].

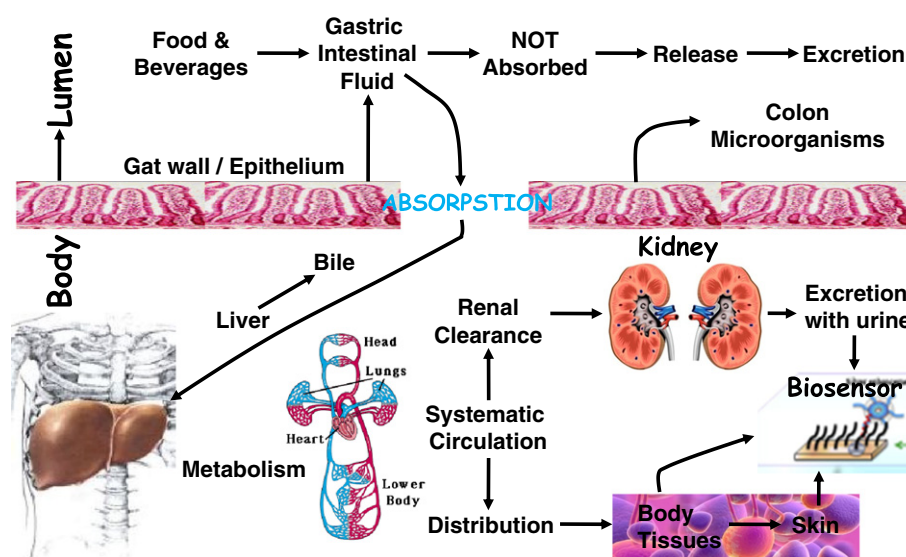


Fig. 3 – Bioactive compound for a target organ. Bioactive compound must reach the target organ at a minimal concentration in order to exert any activity. Consequently, it can determine both biological effect and mechanism of action. Bioactive peptides may be released during the digestion by host enzymes like trypsin or by microbial enzymes. They can be detected by biosensors in urine and plasma.

Other classes of bioactives include flavonoids, phytoestrogens (isoflavones), organosulfur compounds, carotenoids, phenolics, and isothiocyanates. Though these are non-proteinaceous substances, the compounds affect regulatory proteins and processes in cells to elicit beneficial reactions. Many studies conducted on cell cultures have demonstrated the effects of these other food components like butyrate, flavonoid, and genistein on cellular proteins. Apart from all these, interactions between proteins and secondary plant products such as glucinolates and phenolics have been found to confer both non-covalent and covalent modifications [100]. Proteomic methods have been used to study the response of colon cancer cells to quercetin treatment [101] and allowed the discovery and development of several other nutraceuticals.

3.2. Personalized nutrition

As stressed above, through advancement of system biology it now seems quite feasible to propose personalized nutrition or adapting food to individual needs. Priorities, preferences and diet responses vary between individuals due to their genetic makeup, life-style and environment and such information can be delivered by the nutrigenomics and nutripoteomics sectors. Different categories such as pregnant women, the aged, professional athletes, infants, and people recuperating from illness and syndromes have been singled out by the nutritional community to adapt diets specifically for their personalized needs and health demands. Implementation of proteomic and other post-genomic tools is an important step towards more detailed understanding of the complex biological systems that control physiology and pathology of living beings [102]. This widespread conviction stems from the scientific evidence that numerous clinical, physio-pathological and epidemiological studies have underlined the detrimental or beneficial role of nutritional factors in complex inflammation-related disorders such as allergy, asthma, obesity, type 2 diabetes, cardiovascular disease, rheumatoid arthritis, and cancer [103]. Nutrition, in fact, has a strong influence on immune status, development, and decline. Modern immune-modulating nutrition accompanies the consumer through their life stages and styles.

Cultural and olfactory preferences exist between individuals that are taken into consideration by food developers. The genetic and proteomic variations in humans form the final level of personalized nutrition, adapting food to personal genotyping results and no other phenotypic data could convey the same information. This will highlight the genetic predisposition to diseases, allergies, intolerances and metabolic conditions that might otherwise not be discerned [104].

Many chronic diseases such as cancers are caused by genetic, environmental, and life-style factors including diet [105]. The dynamic nature of the proteome in different cellular environments and tissue types produces variation in their contents and kinds in stress, diseased conditions, or drug treatments. Thus, a crucial step in identifying the proteins involved or modified under particular conditions may be to compare the proteome in varying conditions. Single nucleotide polymorphisms which are the most common source of human genetic variation are also factors for the differences in metabolism and sensitivity of individuals to certain diets.

An emerging field concerns personalized nutrition, which is taking the functional food and nutraceutical development one step further by considering the individual predisposition and thus susceptibility. It can be expected that the future omics-based human nutrition research can provide personalized dietary recommendations for disease prevention. Moreover, nutritional proteomic biomarkers must be interconnected with other genomic and genetic markers because with nutrition, consumers want to optimize some aspects of their health without compromising others. By understanding the genotype of a person, personal nutritional solutions possible for the genetic variant could be drawn in the near future. Personalized nutrition is a conceptual analogue to personalized medicine and means adapting food to individual needs.

4. Nanoproteomics

4.1. Defining nanoproteomics: a true marriage of nanotechnology and proteomics

To better understand proteomes and to enable new biomarker discovery, new tools need to be developed by combining the proteomics with other technologies such as nanotechnology. In this context, the integration of nanotechnology and proteomics has led to the development of nanoproteomics, which offers significant advantages over existing proteomic techniques. To name a few, nanoproteomic not only provides a robust analytical platform for real-time, highly sensitive, selective, and low-cost detection of low-abundance and high-dynamic range proteins by enabling multiplexing and high-throughput analysis of low-volume samples [11,106], but it also enables discovery of new biomarkers [107]. It is notable that over the past decade, the scope of nanotechnology has widened to include applications in biological sciences. Nanotechniques have now started to offer a broad spectrum of highly innovative technologies to satisfy the high-throughput demands of proteomics.

From the above description of nanoproteomics, as typically defined in the literature, it may appear that nanoproteomic is a one-directional marriage between nanotechnology and proteomics, wherein although the material science and newly discovered nanotechniques regularly feed into proteomic research, the benefits of this merger to the nanotechnology field is rather non-apparent. However, we argue that it is not the case and there is a true symbiotic relationship between these two apparently diverse fields. This is clearly reflected from the history of integration between nanotechnology and biotechnology. While nanobiotechnology originally focused on the applications of nanoscience discoveries towards biotechnology, it has only been recently that a parallel surmounted growth in the field of bionanotechnology and biomimetics has benefited from the applications of biological science in nanotechnology [108,109]. This growth in bionanotechnology has resulted from the observations by material scientists that the mother-nature has evolved numerous nano- and microscale functional assemblages of proteins, nucleic acids, and other organic biomacromolecules to perform complicated tasks [110]. This ability of biological systems is not restricted to the synthesis of organic molecules, as natural systems are equally capable of efficiently synthesizing and assembling a variety of

elegant functional inorganic nanomaterials with high precision using ingenious strategies, which are overwhelming and daunting for material scientists to emulate in their laboratories [108,111]. A few examples include magnetic nanoparticles synthesized by magnetotactic bacteria [112], siliceous nanomaterials formed by diatoms and radiolarians [113], and gypsum and calcium carbonate nanostructures synthesized by S-layer bacteria [114]. The inspiration from mother-nature led to the development of new biological synthesis routes for nanomaterial synthesis using a variety of those microorganisms that are not typically known to create these inorganic materials in their natural habitats [108,110,111,115,116]. Such recent mergers of bio- and nanotechnology boundaries have enabled Bansal's group to discover the possibilities of hitherto unknown proteins such as silver ion reductase [117] and copper ion reductase [118] that may act as new biomarkers for identification of certain microorganisms. More so, the same research group has identified that the nanoparticle producing ability of certain microorganisms may either be a genus-wide phenotypic characteristic independent of environmental influence or a species-specific attribute [119]. This observation has created new possibilities that the difference in the nanoparticle producing ability of different microorganisms may allow nanoparticles to be employed as unique biomarkers for these organisms. Notably, biological routes of nanomaterial synthesis have reached to a stage now where more focused involvement of genomic and proteomic approaches appears to be crucial for the further growth of this field. Recently, in a fascinating study, genomic techniques resulting in phytochelatin synthase and metallothionein expressing recombinant *Escherichia coli* were used for the synthesis of a wide range of different nanomaterials including semiconductors, noble metals, magnetic nanoparticles, monoelectric alkali earth, dielectric earth, and rare earth fluoride materials [120]. Similarly, taking lessons of molecular recognition, self-assembly and DNA manipulation from biology, novel polypeptides that can specifically bind to selected inorganic nanomaterials, were genetically engineered using phage-display technologies, thereby contributing to a new field of molecular biomimetics [121]. These genetically-engineered proteins for inorganics (GEPs) may overcome the ongoing challenge of the assembly of functional nanomaterials, which have important implications in the growth of nanotechnology. From these examples, it is clear that it is not only nanotechnology that contributes to the field of genomics and proteomics, but the latter also continue to feed in the field of nanotechnology, albeit with a slower pace. The coming years will see the full potential of this one-sided appearing alliance between nanotechnology and other omics-based biological fields, thereby further resulting in the benefits of a true symbiotic marriage and evolution of new fields such as 'genonanomics' and 'proteonanomics'. However, in the specific context of this review, nanoproteomics may be defined as an enabling nanotechnology that addresses the challenges faced by the proteomic community to have a better understanding of the proteomes.

4.2. Nanoproteomics as an enabler for biomarker discovery

Since proteins are an integral part of foods and beverages, a reliable proteomic analysis of foods and beverages with respect to their traceability, quality, safety, and nutritional

value is becoming increasingly important. Since most biological methods of proteomic studies are time consuming, cumbersome, complex, and need large sample volumes, with the advancement of proteomics, it is indispensable to develop new technologies for rapid high-throughput protein analysis. Moreover, one of the critical issues in the food security and safety is the availability of rapid proteomic analysis tools for biomarkers. Nanotechnology is poised with tremendous capabilities in the food and beverage sector by providing solutions to food quality and safety. It should however be recognized that most of the newly discovered nanotechnologies have hitherto been employed for biomedical and diagnostic applications [107,122], with a limited focus on their implications in foods and beverages. However, these biodiagnostic platforms can be easily translated to the food and beverage industries to verify the microbiological and chemical safety of the products or the environment. This can be achieved by nanotechniques to assist with efficient analysis of already known biomarkers, as well as by enabling development of new nano-biomarkers. Nanoparticles can be particularly important for such biomarker discoveries and bioanalysis of foods and beverages as the surface of nanoparticles can be controllably tuned to be highly reactive and/or towards exhibiting selective preference towards proteins due to reactive thiol and amine groups present in the biomacromolecules [123–125]. This in-turn enables nanoparticles to be used as baits for fishing biomarkers usually present in foods and beverages in significantly low quantities. Additionally, nanoparticles possess extremely high surface area to volume ratio that further makes them ideal to sequester high amount of proteins available for proteomic analysis. Owing to the feasibility of facile and selective surface modification of nanoparticle surface chemistry [126–128], nanotechnology developments provide an excellent opportunity to sequester a particular type of protein biomarker that would be critical in assessment of food and beverage quality. Such applications of nanomaterials are becoming more and more evident from the incorporation of nanoparticles in well-established proteomic platforms such as use of monolith columns with unique nanostructures for efficient milk sample preparation and analysis [129]. Additionally, a single or multiple target protein molecules can be bound to a nanoparticle, which can be used as an affinity probe for matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF)-MS analysis of the target protein. Traditionally, in MALDI-MS analysis, an organic matrix is incorporated to transfer laser energy to the analyte and to provide stability to the analyte against laser radiation. However, the organic matrix introduces background ions and hence compromises the signal-to-noise ratio. Recently, researchers have started considering replacing organic matrix with inorganic nanomaterial surfaces to increase the signal-to-noise ratio of MS [130]. The target-functionalized nanoparticle probes can be utilized for proteomic analysis employing matrix-free direct laser desorption ionization (DLDI)-MS [131]. Moreover, smart nanoparticle designing strategies offer the potential to solve the well-known proteomic challenge, the so-called dynamic concentration barrier that results from the fact that within the same biomaterial, proteins with high-dynamic range varying from millimolar to femtomolar concentrations typically coexist. An example of such approach is the design of core-shell bait

nanoparticles composed of N-isopropylacrylamide hydrogels that can perform four functions in one step in complex biological fluids including molecular size sieving, complete exclusion of high abundance unwanted proteins, target analyte affinity sequestration, and complete protection of captured analytes from degradation [132].

In the context of biomarker measurements, validation, and discoveries, the already available and the newly developed technologies may be considered either those that are reliant on target-analyte interaction or those that may be considered label-free. The label-free techniques offer significant advantage by enabling biomarker discovery in the absence of any prior knowledge of the target biomarker. Although, the conventional proteomic techniques such as immunoassays and protein microarrays are reliant on an external label/tag for biomarker analysis, techniques such as 2-DGE and mass spectrometry (peptide mass fingerprinting (PMF) and liquid chromatography coupled with MS) offer label-free proteome and biomarker analysis. However, these proteomic techniques suffer from resource and time-intensiveness, limited dynamic range, complex separations, complex data analysis, and possibility of false identifications. Nanoproteomics offer solutions to address these challenges by enabling highly sensitive, selective, rapid, low-cost, and high-throughput analysis of foods and beverages. While trying to introduce the above advantages through nanotechnology developments, most of the nanoproteomic discoveries have initially been reliant on label-based techniques employing certain bioreceptors or biological recognition elements such as antibodies, enzymes, aptamers, nucleic acids, biomimetic receptors, bacteriophages, and even whole cells [133], while there has been an increasing emphasis on development of label-free nanoproteomics for biomarker discovery. The nanoproteomic techniques typically involved in foods and beverages include optical, electrochemical, and

mass-based methods; all of which may be further divided into label-based and label-free methods. For further details about these techniques, readers are encouraged to refer to the recently published reviews [133,134]. Additionally, the integration of nanotechnology with existing proteomic tools has resulted in the development of miniaturized platforms for proteomic research such as a nano HPLC-chip coupled with ion trap MS for the differential analysis of bioactive lupin proteins [19], nano-capillary electrophoresis for separation and analysis of a range of bioentities [135], and other separation techniques such as capillary electromigration, microchip, and nano-LC/capillary LC [136]. These miniaturized nanoproteomic platforms have enabled minute quantities of biological samples to be analyzed in a high-throughput manner, thereby addressing one of the major challenges of proteomics.

4.3. Demonstrated applications of nanoproteomics in foods and beverages

Nanoproteomics have been widely employed for biomedical applications for the identification of various biomarkers, however it is only recently that nanoproteomics have started finding applications in foods and beverages. Moreover, even within the field of foods and beverages, although several parameters such as microbial contamination, allergens, toxins, adulteration and traceability of genetically-modified organisms are significant issues of concern, most of the nanoproteomic studies have so far focused on identification of microbial load (Fig. 4). In this review, we have attempted to highlight some of the case studies reflecting potential of nanoproteomics in foods and beverages. Table 1 illustrates the current/potential future applications of nanoparticles and nanoproteomic platforms highlighting different areas of foods and beverages including safety, quality, traceability and

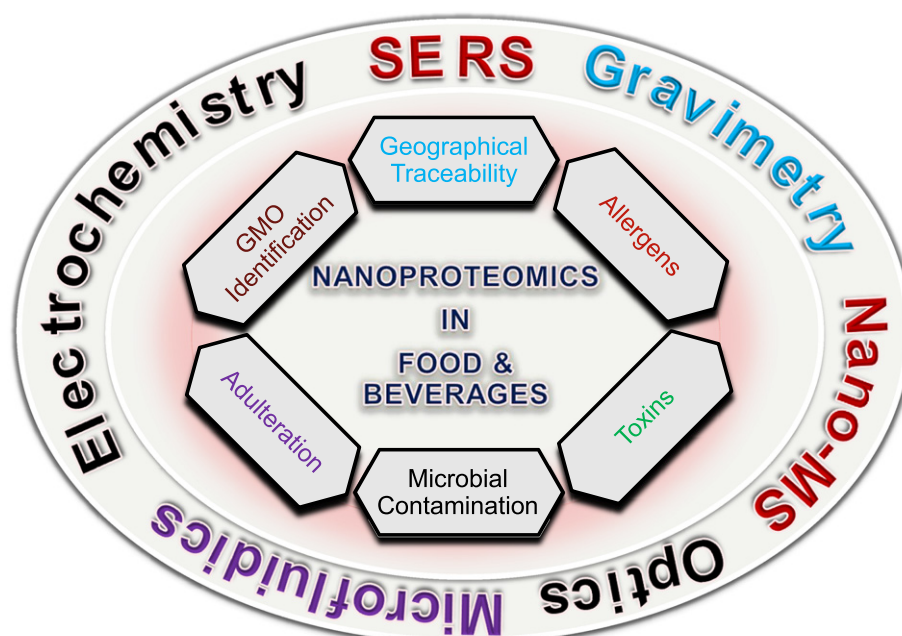


Fig. 4 – Nanoproteomics in foods and beverages. Cartoon depicting the current challenges associated with foods and beverages (inner circle) and some of the nanoproteomic approaches (outer circle) suitable to overcome these challenges.

Table 1 – Nanoproteomics for foods and beverages.

Application area	Nanoproteomic platform *Potential	Nanoparticle type *Potential	Target	Remarks	References
Food and beverage safety					
Plant diseases and food spoiling microbes	*SERS *Nano-MS Drug/gene delivery	Metallic, metal oxides *Multiple Metallic and silica nanoparticles	Detection and biomarker discovery Detection and biomarker discovery Drug/gene delivery	Highly sensitive Highly sensitive Biolytic approach	[159–162] [11,106,163] [164,165]
Allergens	*Nano-immunoassays SPR biosensor	Multiple Magnetic nanoparticles	Detection and biomarker discovery Detection	Immunotechnology approach Rapid and highly sensitive detection of Ara h1 peanut allergen in food	[166] [167]
Human pathogens (e.g. <i>E. coli</i> in lettuce, sprouts and apple juices; <i>Salmonella</i> in tomato, seed sprouts, cantaloupe, mamey apple and orange juices; <i>Shigella</i> in lettuce, scallions, parsley; <i>Brucella</i> , <i>Staphylococcus</i> sp. in milk)	*Nano-MS SERS SPR and other nanomaterials based biosensor *Microfluidics + SERS-based dielectrophoresis nanoplatfrom Electrochemical immunosensing	Metallic, magnetic oxides, carbon nanotubes Magnetic nanopores *Multiple Silver nanoparticle Carbon nanotube	Detection/biomarker discovery <i>Salmonella</i> and <i>Staphylococcus</i> in spinach and peanut butter Detection of microbes in food and other samples Detection of microbes in food and other samples Multiplexed detection of food-borne pathogens in milk	MALDI-MS targets for matrix free ionization. Tailoring of the surface allows selective enrichment of specific proteins and peptides High resolution, ultra-fast, selective enrichment High resolution, ultra-fast, selective enrichment Principles, applications and over view of technology High resolution, ultra-fast Feasibility study	[106,107,122] [168] [169] [157,158] [170]
Other contaminants	SERS *Optical Electrochemistry	Magnetic nanoparticles Au/SiO ₂ nanoparticles Ag nanoparticle coated polystyrene-co-acrylic acid composite nanospheres/ magnetic/gold Quantum dots Gold nanoparticles Iron oxide nanoparticles/ multi-walled carbon nanotubes Gold and nanocomposite planar electrodes	Rapid detection of ricin in milk Detection of parathion in fruits Detection of melamine in fruits and milk Detection of pesticides Detection of melamine Measurement of organophosphorus insecticides in milk and water Glycerol level in wine	High resolution, label free High resolution, label free High resolution, label free Potential applications in food safety Limit of detection is well below the safety limit Sensitive, stable and reusable biosensor	[171] [172] [173,174] [175] [176,177] [178]
				Fast, sensitive, reusable biosensor	[179]

Adulteration	SERS	Silver dendrimers	Adulteration of milk samples with the egg white protein ovalbumin	High resolution, label free	[154]
	Electrochemistry	Copper nanoparticles	Fast differentiation of meats from fifteen animal species	No derivatization or extraction steps, rapid	[180]
Food and beverage quality					
Composition/food & beverage authentication	SERS	Graphene and silver nanocomposite	Detection of prohibited colorants in food	High resolution, label free	[181]
	Electrochemistry	Acetylene black nanoparticle-modified electrode	Ponceat 4R and tartrazine in soft drinks	Method is sensitive, rapid, simple and feasible	[182]
		Gold nanoparticles	Simultaneous determination/estimation of multiple food antioxidants in edible oils	Feasibility study	[183]
Drought resistant plants	Nano-MS	Magnetic graphene oxide and others	Biomarker discovery	Reduced sample volume and improved signal to noise ratio, selective enrichment	[106,107,184]
Salinity and osmotic stress resistance	Nano-MS	*Nanoparticle affinity matrices	Biomarker discovery in plants under stress through proteomics	Improved signal to noise ratio, selective enrichment	[185,186]
Temperature resistant	*Nano-MS	Magnetic graphene oxide and others	Biomarker discovery	Reducing sample volume and improving signal to noise ratio	[106,107,184]
Metal exposure	*Nano-MS	Magnetic graphene oxide and others	Biomarker discovery	Reducing sample volume and improving signal to noise ratio, selective enrichment	[106,184]
Food and beverage traceability					
GMO identification/production	*Nano-MS and others	Gold nanoparticles, carbon nanotubes, liposomes	Plant biotransformation	Novel nanotechnology strategies	[106,187]
	SERS-barcode biochip nanosensors	Silica coated gold nanoparticles	Detection of transgenic rice varieties	Real-time PCR comparable detection limit	[188]
	Optical	Gold nanoparticles	Detection of transgenic soy crop	Rapid and sensitive	[189]
Gold nanoparticles		Detection of transgenic crops through dynamic light scattering	Rapid, ultra-sensitive and label free	[190]	
Origin/selection	Nano-MS	Gold nanoparticles	Detection of selectively captured glycopeptides from peptide mixtures of food sample	Selective enrichment	[191]

associated technology. Latest examples of application of nanoparticles and nano-devices in the area of foods and beverages have been cited. Additionally, wherever the nanoproteomic technology has been used in disciplines other than foods and beverages, their potential use in food science is predicted through citations of research from other fields and discussed in the following sections. The table is by no means exhaustive and gives a flavor of the state-of-the-art technology perspective to the readers.

A common method that employs reflectance spectroscopy for the pathogen detection is surface plasmon resonance (SPR) spectroscopy. SPR is capable of detecting minor changes in the refractive index that occurs when an analyte or cell binds to the receptors on the SPR substrate surface. SPR-based nanoproteomic platforms have been employed for the detection of food-borne pathogens such as *Listeria monocytogenes* [137], *Salmonella* spp [137], *E. coli* O157:H7 [138] and *Campylobacter jejuni* [137]. Recognizing that a successful nanoproteomic platform must distinguish a target analyte from a complex mixture, a multi-channel SPR platform was developed for the quantitative and simultaneous discrimination of the four bacterial species viz. *E. coli* O157:H7, *Salmonella choleraesuis*, *L. monocytogenes*, and *C. jejuni* [137]. Optical fibers that are based on the principle of total internal reflectance have also been employed for pathogen detection in the food samples. For instance, while a fiber optic portable nanoplatform coupled with fluorescence resonance energy transfer (FRET) was employed for fast detection of *Salmonella typhimurium* in ground pork sample [139], a portable evanescent-wave fiber optic platform was developed to detect *E. coli* in ground beef samples [140]. Similarly, a fiber optic SPR platform was able to detect ng/mL concentration of *Staphylococcal enterotoxin B* in less than 10 min [141]. Electrochemical nanotechniques such as amperometric, potentiometric, impedimetric, and conductometric that are based on the observed parameters such as current, potential, impedance, and conductance, respectively have also been applied for foods and beverages. Micheli and co-workers employed screen printed electrodes to develop an amperometric platform to detect aflatoxin M1 in milk with a detection limit of 25 ppt and with a working range between 30 and 160 ppt [142]. Yang and colleagues used interdigitated microelectrodes as an impedimetric platform for rapid detection of viable *S. typhimurium* [143]. More recently, Pal and colleagues developed a direct charge transfer conductometric platform by coupling it with sandwich immunoassay for the detection of 35–88 CFU/mL *Bacillus cereus* in various food samples with a detection time of 6 min [144].

Mass sensitive gravimetric platforms based on quartz crystal microbalance (QCM) and surface acoustic wave (SAW) nanodevices have also been employed for the detection of food-borne pathogens. *S. typhimurium* in chicken meat samples were detected using QCM immunosensors with a detection limit of 10^2 CFU/mL [145], and SAW-based nanoplatform was used for rapid (80 s) detection of *E. coli* O157:H7 [146].

Development of nano-enabled electronic noses has also received considerable attention as shown by identification of meat samples infected with *S. typhimurium* at a population concentration level $\geq 0.7 \log_{10}$ CFU/g [147]. Also, nanoplatform based on electronic conducting polymers was reported for detection of fish freshness [148].

More recently, a nano-enabled surface enhanced Raman spectroscopy (SERS) technique is finding its way into foods and beverages, as it is a metabolic fingerprinting technique capable of measuring the unique biochemical fingerprints of a particular organism or biological samples within minutes, with minimal sample preparation [149,150]. Since each molecule has a unique, distinguishable and signature Raman spectrum, Raman spectroscopy is capable of generating new spectroscopic biomarkers of different food and beverage samples, more importantly without the requirement of any external label. Moreover, Raman spectroscopy can simultaneously identify multiple targets in a sample, thereby providing an attractive solution for the multicomponent analysis in food and beverage samples [151]. Also since water molecules do not show Raman signature, this technique provides an ideal platform for analysis of biological samples. However, an inherent limitation associated with Raman spectroscopy is its low sensitivity due to poor Raman cross-section of 1 per 10^8 molecules. Therefore, Raman spectroscopy has not hitherto been broadly applied for biomarker analysis and discovery of foods and beverages, except in limited cases, where Raman spectroscopy was coupled with principal component analysis (PCA) and chemometrics to enable differentiation between different food microorganisms [149,151].

The development of nanotechnology has significantly contributed to Raman spectroscopy technique as it was recognized that this low sensitivity limitation of Raman spectroscopy can be overcome if a suitable nanostructured surface is utilized as a substrate to perform Raman spectroscopy [152,153]. Therefore, in the presence of suitable nanostructures, SERS can improve the Raman sensitivity to 10^{15} times, leading the potential of this technique for single molecule or single cell detection. This has enabled an ultra-low sensitive Raman spectroscopy technique to be transformed to a super-high sensitive SERS technique. SERS technique using dendritic silver nanoparticles was recently employed to identify the adulteration of milk samples with the egg white protein ovalbumin with detection limit of 5 $\mu\text{g/mL}$, within 30 min [154]. Using different nanomaterials, SERS technique has also been employed to barcode bacterial cells, which enabled differentiation of different bacterial species including six species of *Bacillus*, two species of *Mycobacterium*, *E. coli*, and *S. typhimurium* [155]. A SERS-based portable Raman system was developed for identification of foodborne pathogenic bacteria and unambiguous identification of *L. monocytogenes*, *E. coli* O157:H7 and *Salmonella enterica* was demonstrated [156]. More recently, Bansal's group demonstrated that microfluidic-based dielectrophoresis nanoplatforms can be developed that have the potential to identify toxins produced by lethal organisms such as *Bacillus anthracis* within less than a minute [157]. The same group has also developed new algorithms for analysis of Raman spectra arising from complicated biological samples having a variety of analyte molecules, thereby taking the capability of SERS for enabling biomarker development to the next stage [158]. These developments in the field of SERS technology signify the potential of multidisciplinary approaches coupling nano-engineering principles with modeling and SERS technology for highly selective and sensitive detection of various biological entities.

4.4. Nanoproteomics: a promising future

As nanotechnology continues to play an important role in the growth of different biological disciplines, it will undoubtedly make significant contribution towards promoting proteomic research in the future. Looking at the earlier discussed nanoproteomic case studies which indicate its current status pro and where nanoproteomics may be in the future, two trends can be clearly identified — evolutionary growth versus revolutionary growth. The evolutionary trends will continue to feed into existing proteomic techniques to improve their capabilities (e.g. miniaturization of MS-based platforms and incorporation of nanoparticles in advanced separation techniques). On the other hand, the revolutionary trends will lead to the development of new technologies, such as SERS-based platforms, which will enable new biomarker discoveries. Technologies such as SERS will not only uncover the existing biomarkers with high sensitivity, but it will also enable development of new label-free biomarker profile of different biological samples. SERS-based and other similar technologies will most likely fundamentally redefine the biomarker discovery platforms, as they will enable spectroscopic signatures of different foods and beverages to be employed as biomarkers. This will mean that any adulteration, allergen introduction or microbial contamination of foods and beverages will be effectively traced to the minuscule level within fraction of time with high selectivity.

5. Concluding remarks

Genome-driven technologies including proteomic and system biology have revolutionized the field of biomarker discovery and applications in foods and beverages. Examples provided in this review demonstrate the power of proteomics and translational proteomics in addressing food and beverage safety. A number of proteomic techniques are being developed for fast and sensitive detection of biomarkers. One example is the quantitative proteomics, allowing the rapid identification and quantification of stress and tolerance-related proteins. Moreover, understanding the dynamics of expression and PTMs of involved proteins, and gaining direct insight into their function can provide essential information that for example, can be rapidly applied to engineer stress tolerant crops with novel traits through biomarker selection and transgenic strategies.

Nanoproteomics are emerging new research areas for rapid and sensitive development and detection of suitable biomarkers for foods and beverages. Provided examples of its applications demonstrate that nanoproteomics have promising future for food and beverage safety. Yet, this technology needs to be optimized for its different applications and adapted widely in industries, government, and non-government sectors. A common theme for all biomarker nanoplatforms is to not only reduce the time of analysis but also ensure a low percentage of false negatives and positives. Ideally, the employed nanotechnology should be quantitative, although in many instances, qualitative tests will suffice, provided the sensitivity (detection limit) is sufficient for the target. When developing nanoproteomic approaches, it is imperative to appreciate the end application and thereby tailor the nanodevice characteristics.

Commercially, it might be desirable to have a single nanoproteomic platform that can be used to screen all microbes and biomarkers in any matrix. However, in reality, each microbial type and food matrix has different characteristics that need to be considered when selecting a sample preparation and diagnostic platforms. For instance, a key point often overlooked when developing nanosensor devices is the levels of pathogen or toxin targets expected to be present in the sample. In clinical samples, the allowable limit for the target pathogen or toxin might be higher, whereas in foods, it is required to be present at low numbers (1 CFU or ng per 25 g of sample). Similarly, for medical diagnostics, there is a need to develop miniaturized (lab-on-a-chip) diagnostic platforms requiring very small sample volumes (μL). On the contrary, it is not always necessary to use low sample volumes for foods and beverages. Hence, nanoproteomic approaches in foods and beverages should focus on devices that enrich samples to increase cell numbers or concentrate the target, as use of low amount of samples ultimately reduces the overall sensitivity of nanoproteomic devices.

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