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Challenges hindering the commercialization of nutraceuticals derived from agri-food by-products

Renan Danielski

Department of Biochemistry, Memorial University of Newfoundland, St. John's, NL, Canada A1C 5S7. E-mail: rdanielski@mun.ca
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Abstract

Several agri-food by-products carry a significant amount of bioactive compounds and could potentially be transformed into nutraceuticals within the circular economy framework. However, the full realization of this potential is hindered by logistics, technological, biological, and regulatory challenges, slowing down the development of a robust nutraceutical market. The present article discusses the need for innovative solutions to optimize waste collection and transportation. The technological challenges in extracting and preserving bioactive compounds call for advancements in unconventional extraction methods and encapsulation approaches. Biological challenges, particularly regarding the bioaccessibility and bioavailability of bioactive compounds, underscore the importance of tailoring delivery methods for optimal efficacy. In addition, selected regulatory aspects need to be highlighted in order to clarify the need for harmonization in ensuring the safety and efficacy of nutraceuticals. Despite challenges, the potential rewards include health benefits, economic growth, and environmental sustainability, driven by the pivotal role of scientific research and interdisciplinary collaboration to realize the vision of a circular economy in the agri-food sector.

Keywords: Logistics; Bioavailability; Phenolic compounds; Encapsulation; Regulation.

1. Introduction

The circular economy concept has been introduced as an environmentally-friendly alternative to the classic linear economy approach (produce, use, and dispose). Within the framework of circular economy, minimization of material consumption and waste generation, as well as recycling and by-product utilization/upcycling are key steps in achieving a more sustainable model. The agri-food industry is a major contributor to global waste generation. Food losses can occur during all stages of the supply chain, including post-harvest management, processing, storage, transportation, retailing, and household consumption. It is estimated that agri-food discards account for 5 billion tons of biomass residues per year globally, being responsible for 3.3 billion tons of carbon dioxide emission. Currently, the linear economy model predominates in this sector, meaning that by-products from the food industry are usually disposed in landfills, dumped in the ocean or incinerated. Common alternatives to processing waste reuse include their application as soil fertilizers and animal feed, which are not ideal solutions when we consider the bioactive potential of some of these by-products (Torres-Valenzuela et al., 2020).

Among agri-food industries, the fruit and vegetable segments are among the leading sectors in terms of waste generation, which usually come in the form of skins, seeds, stems, barks, and leaves. The Food and Agriculture Organization (FAO) of the United Nations estimates that from the total global production of fruits and vegetables, around 45% is wasted, where 21% represents food loss from harvesting to distribution (FAO, 2019). At an industrial level, zero waste processing has been proposed as a strategy to reduce residue generation by a complete utilization of the raw material. For instance, if a fruit is processed to obtain frozen pulp, the generally discarded fractions (skins, seeds, leaves) would be used in other production processes, generating alternative high value-added products. This approach is advantageous both from an economical and a sustainable standpoint, as more revenue streams could be generated for stakeholders and the

Table 1. Health-promoting effects of nutraceutical ingredients obtained from agri-food by-products

Nutraceutical ingredient	Active compounds	Health effects	Reference
Peanut skin	Quercetin, vanillin, catechin, epicatechin, epigallocatechin gallate, B-type proanthocyanidin, quinic, gallic, protocatechuic, caffeic, coumaric, ferulic, and ellagic acids	Free radical scavenging, antidiabetic, anti-obesity, antiproliferative effects toward colorectal cancer cells	Cordeiro-Massironi et al. (2023)
Tannat grape skin	Phenolic extract	Antidiabetic, anti-obesity, anti-inflammatory effects toward RAW 264.7 cells	Fernández-Fernández et al. (2019)
Tomato skin and seeds	Lycopene	Free radical scavenging, ferric reducing power	Silva et al. (2019)
Apple pomace	Epicatechin, gallic acid, quercetin	Anti-inflammatory and anti-platelet properties	Tsoupras et al. (2021)
Shrimp by-products (Cephalothorax and abdominal parts)	Astaxanthin and bioactive peptides	Angiotensin I converting enzyme (ACE) inhibition, cellular antioxidant activity on 3T3 cells	Messina et al. (2021)

environmental burden of waste disposal would be mitigated. Nevertheless, the implementation of this model is still hindered by the high costs associated with transportation and conservation of agri-food by-products to processing plants. In such a scenario, research on the potential of these discarded fractions is essential in order to demonstrate that earnings stemming from the reuse of food waste could offset the initial costs (Singh and Krishnaswamy, 2022). Nayak and Bhushan (2019) mention the extraction of value-added components, such as polyphenols, as one of the possible approaches that can be adopted for valorization of food by-products. Such molecules could serve as the basis for the production of nutraceuticals and functional foods. Nutraceuticals are capable of providing health benefits beyond basic nutrition and are used in the medicinal form. This product category has played a pivotal role in health promotion, being associated with a reduced incidence of metabolic syndrome conditions such as obesity, type 2 diabetes, some types of cancers, and cardiovascular ailments, as well as decreased risk of neurodegenerative diseases and enhanced lifespan and health. Table 1 shows examples of nutraceutical ingredients prepared from agri-food by-products and their effects on health.

The global market for nutraceuticals reached US$ 412 billion in 2020, accounting for over 25% of the pharmaceutical industry's value. Developed countries such as the United States, Japan, and Germany are the main drivers of the nutraceutical market. Besides, fast growth is projected for developing countries (e.g., China, India, Brazil) in the next few decades (Grand View Research, 2020). The increase in consumer awareness about the relationship between diet and health, as well as ageing populations, increasing healthcare costs, increasing distribution channels, and growth of preventive medicine are key factors in the popularization and expansion of the nutraceutical segment (Chopra et al., 2022). Nevertheless, logistics, technological, biological, and regulatory hurdles still hinder the widespread achievement of the nutraceutical market's potential, especially in what comes to the reuse of agri-food residues as bioactive-rich ingredients for nutraceuticals. Therefore, this contribution discusses some of these challenges, from the complex agricultural waste logistics to the current regulatory framework on nutraceutical products.

2. Logistics challenges

Food loss is defined as the portion of edible food lost during production and distribution, while food discarded by retailers and consumers is categorized as food waste (FAO, 2019). Although both terms are used interchangeably, it is important to establish the correct nomenclature as circular economy approaches are usually designed to tackle issues at the industrial level. Therefore, food loss will be the focus of this article in what concerns the upcycling of agricultural by-products. Food loss can be hampered either by preventing its generation, which is believed to be the preferable approach, or by adding value to discarded materials from food production (Teigiserova et al., 2020). When food loss prevention is not possible, giving a proper destination to agri-food by-products is most important in order to avoid the environmental implications of landfill dumping, incineration, and other similar waste disposition strategies (Kusumowardani et al., 2022).

Common solutions found by several agri-food companies include their use as compost and animal feed. Although this is a valid short-term solution, it misses the potential of turning these residual materials into high value-added products that can represent new revenue streams and business opportunities for this sector. For instance, processing guava fruit for the production of juice and frozen pulp generates around 30% of loss in the form of a uniform fraction containing seeds, skins, and residual pulp. This lost fraction is an outstanding source of lycopene and phenolic compounds, including several ellagic acid derivatives, with demonstrated *in vitro* ability to ameliorate biological markers associated with type 2 diabetes, obesity, atherosclerosis, and mutagenesis (Danielski and Shahidi, 2023). As such, guava waste fraction could be transformed into a potent bioactive ingredient for the development of nutraceuticals. However, the pathway from waste collection to nutraceutical production is not currently streamlined in most locations, encountering several barriers along the way. Although the theorical framework of circular economy is being established at a fairly quick pace, practical aspects still need to be sorted out before these proposed solutions become a reality.

The first hurdle to be overcome concerns the intricate agri-food waste logistics. The collection of food residues can be challenging especially when large amounts are required. In this case, waste must be procured from several different sources (e.g., farms, processing plants, distribution centers) located within a short distance from each other due to the high perishability of the material and to mitigate transportation costs. For transportation, specialized vehicles and infrastructure to manage the collected material are needed due to the high susceptibility to microbial spoilage. In addition, flexible logistic plans should be in place to account for the variability in the types and amounts of waste generated, as these factors are common when dealing with agricultural feedstock. In order to streamline the process, technological tools such as sensors and tracking systems to monitor and optimize logistics and traceability would be essential. It can be inferred by this brief description that several stakeholders would be involved in the acquisition, collection, transport, and management of agri-food by-products for upcycling. This would require collective effort and effective communication between the parties involved, with well-defined roles, clear objectives, and awareness about the benefits of waste upcycling (Galanakis, 2013; Lordan et al., 2021). Therefore, the development of educational programs to be delivered to all stakeholders involved should be the first step towards achieving a circular economy model within this sector.

3. Technological challenges

The transformation of agri-food by-products into nutraceuticals holds several technological challenges, which starts with the recovery of bioactive compounds from the residual material. For that, a number of extraction protocols are available and the choice for a specific method generally depends on the nature of the matrix (fresh or dehydrated), targeted compounds, availability of equipment and chemicals, and preliminary optimization of extraction conditions, among others. The procedure may be conducted using a fresh sample or a drying step may be included. The most frequently used dehydration techniques are oven-, spray-, and freeze-drying. De Torres et al. (2010) studied the influence of the drying method on phenolic composition of grape skin. For that, freeze-drying was compared with oven-drying at 60 °C for 24 h. Freeze-drying was able to preserve the identified phenolics better, showing higher concentrations when compared with oven-dried samples. Oven-drying decreased anthocyanidins by 39% and flavonols by 43%. The same drying techniques were compared by Nunes et al. (2016) when producing guava powders. Both processes promoted loss of phenolic compounds. Nevertheless, the distribution of soluble and insoluble phenolics differed between the procedures. Oven-drying led to the release of a higher amount of flavonoids while presenting a higher degradation rate of non-flavonoids. At the same time, oven-dried powders showed higher antioxidant capacity than freeze-dried ones, especially when oxygen radical absorbance capacity (ORAC) assay was employed, which led to the conclusion that flavonoids were the main contributors to antioxidant activity in this case. The authors stated that distinct phenolic classes would be differently affected by drying processes, which has been observed and supported by other similar studies.

The extraction of bioactive compounds can be performed by conventional or unconventional techniques. Conventional techniques involve the addition of a solvent system to the sample, with further leaching of the target compounds. Soxhlet and maceration are widely used conventional extraction techniques for isolation of phenolics. However, some of the drawbacks of conventional extraction involve excessive use of organic solvents, difficulty of scaling up, and time-consuming protocols. Therefore, alternative methods have been studied in order to minimize these constrains. Unconventional extraction relies on the increase of extraction efficiency to make it possible to minimize solvent use and shorten extraction times, at the same time as increasing extract yield.

Supercritical fluid extraction (SFE), microwave-assisted extraction (MAE), pressurized liquid extraction (PLE), pulsed electric field (PEF), high-pressure processing (HPP), steam explosion (SE), and ultrasound-assisted extraction (UAE) are commonly used non-conventional approaches. Recently, UAE has gained popularity as an efficient method to extract carotenoids and phenolic compounds. Some of its advantages include increased bioactive yield with mild/low temperatures, simplicity, low-cost, and short extraction periods (usually around 20–30 min, depending on the sample). Acoustic cavitation is the principle behind UAE, where microbubbles form and collapse, generating localized extreme temperatures (5,000 K) and pressure (1,000 atm). This effect produces increased shear energy waves and turbulence in the cavitation zone, rupturing the plant tissue and enhancing solvent penetration (Chemat et al., 2012). Additionally, UAE can be coupled with other methods acting as sample pre-treatment for the release of target substances covalently bound to other components of the feedstock. For instance, HPP and SE have been efficiently utilized to release insoluble-bound phenolic compounds from sea cucumber by-products (Hossain et al., 2022) and grape pomace (Cui et al., 2023), respectively, increasing the yield of total phenolics and optimizing the extraction process.

Nevertheless, after being extracted from their natural sources, bioactive compounds become exposed to detrimental factors during processing and storage, such as temperature fluctuations, light and oxygen exposure. These conditions can oxidize and degrade bioactives, causing loss of activity. Thus, finding ways to preserve these molecules so they can perform their intended action represents another technological challenge. In this regard, encapsulation appears as one of the most promising solutions. Encapsulation can be defined as a process where a food-grade wall material envelops a target substance. This is usually done to provide a barrier against environmental factors that could degrade these compounds and, consequently, reduce/deplete their bioactivities. Therefore, encapsulation can be perceived as a tool to extend the self-life of products where such compounds exert a key function. Another positive outcome is the controlled release of bioactives throughout the digestive system promoted by encapsulation, increasing the bioavailability and expanding the health-promoting aspect of bioactive compounds. Additionally, active ingredients/molecules that confer undesirable aroma and taste to food products can have those characteristics masked by encapsulation (Marcillo-Parra et al., 2021).

Several encapsulation methods are available, depending on the bioactive entrapment methodology and wall material used. For bioactive protection, nanoencapsulation and microencapsulation are commonly used. While the former encompasses capsules with particle size ranging between 10 and 1,000 nm, microencapsulation produces capsules of 3–800 μm and is the basis for the production of a myriad of food ingredients. Microencapsulation techniques can be based on physical (e.g., spray drying, free drying, extrusion, fluid-beat coating), physicochemical (spray cooling, ionic gelation, solvent evaporation, liposome entrapment, coacervation), and chemical (interfacial polymerization, molecular inclusion cross-linking) processes (Marcillo-Parra et al., 2021). Pashazadeh et al. (2021) promoted the microencapsulation of phenolics extracted from maize waste by using maltodextrin as a wall material while testing three drying techniques – freeze drying, spray drying, and microwave drying. Among them, freeze drying displayed the highest retention of phenolics in the capsules compared to the original non-encapsulated extract. The preservation was especially high for protocatechuic, *p*-coumaric, and salicylic acids, as well as catechin. Concurrently, nanoencapsulation has been shown to effectively safeguard the stability of bioactive molecules. However, besides presenting higher complexity and cost than microencapsulation, safety concerns are still an issue for some nanoencapsulated materials with respect to cell membrane permeability and effect on biological matrices (Galanakis, 2013).

4. Biological challenges

As nutraceuticals are intended for health-boosting purposes, their biological efficacy and safety are crucial for commercialization and market success. Target substances for nutraceutical development should exhibit satisfactory bioaccessibility (amount of target substance released from the food matrix that becomes available for intestinal absorption) and bioavailability (amount of active substance absorbed and detected in the target site in relation to the total amount orally ingested) (Shahidi and Peng, 2018). Therefore, in order to act as a potential tool for fighting chronic diseases, these compounds should be readily released from their matrix, be absorbed and travel to the sites where the compound or its metabolites can carry out their functions. However, the absorption rate of bioactive molecules is highly variable, representing another barrier to the production of nutraceuticals (de Camargo et al., 2018; Shahidi and Yeo, 2016).

Carotenoids can be reduced by up to 40% after *in vitro* gastrointestinal digestion, with even higher losses observed after colonic fermentation (up to 96%). This means that the majority of carotenoids consumed in the diet may not be efficiently released from their matrices in order to be absorbed and travel to the target tissues to exert their biological activities. However, adjustments regarding the delivery method for carotenoids may greatly enhance their oral bioavailability, such as the use of lipophilic matrices to package carotenoids. As fat-soluble molecules, carotenoids dissolved in lipophilic media can travel through the gastrointestinal tract in a micelle form, going through the same digestive route as dietary fat. For this reason, the combination of carotenoids with fat-soluble vitamins (D, E, and K) reduces their bioaccessibility due to the competition for micellization and cellular uptake by apical transporters. The delivery of carotenoids in a nutraceutical form, when enveloped in a compatible fat-soluble material, is a valid strategy to enhance their bioaccessibility. Once they are effectively released into the gastrointestinal tract, carotenoids can be absorbed in a relatively easy manner due to their capacity to cross the nonpolar epithelium bilayer membrane (Xavier and Mercadante, 2019).

The same cannot be said for phenolic compounds. The great majority of polyphenols is of polar nature, meaning that their ability to cross biological membranes and be efficiently taken up by the enterocytes is greatly diminished. Recently, structural modification of phenolic compounds has been proposed to increase their lipophilicity. For instance, Oh et al. (2021) has used esterification to produce fat-soluble quercetin derivatives (C3:0-C22:6) and demonstrated similar or better antioxidant activity and oxidative protection to supercoiled DNA and LDL-cholesterol when compared to quercetin's original form. Additionally, phenolic biaccessibility can be impaired by the occurrence of insoluble-bound phenolics, covalently bound to cell wall macromolecules (e.g., pectin, cellulose, structural protein). Such compounds are not released from the matrix during the digestive process and are subjected to colonic fermentation. In cereals and legumes, insoluble-bound phenolics can represent up to 60% of all phenolic content (Shahidi and Yeo, 2016). Microencapsulation and nanoencapsulation have also been extensively studied as a tool to increase the bioaccessibility and bioavailability of phenolic compounds. However, most studies are conducted *in vitro*, with a lack of evidence stemming from animal studies and clinical trials (Abuhassira-Cohens et al., 2022).

5. Regulatory challenges

The nutraceutical definition presents an overlap between food, dietary supplements, and pharmaceuticals, challenging how they are positioned within each regulatory framework. Consequently, the nutraceutical concept can present discrepancies between countries, affecting how they are approved and regulated. This lack of unity may result in ambiguity and inconsistency when it comes to the international commercialization of this product category. For instance, some countries do not mention the term nutraceutical in their current established regulations (Chopra et al., 2022; Santini et al., 2018). The European Food Safety Authority (EFSA) does not differentiate between dietary supplements and nutraceuticals. The latter needs to comply with the same standards set for medicinal products, with parameters including efficacy, safety, and quality testing. Also, nutraceutical brands intending to make health claims on the product's label must comply with Regulation EC 1924/2006, which aims to provide easy-to-understand information and ensure safety and efficacy to consumers (European Commission, 2006).

Conversely, in the United States, nutraceuticals are monitored by the Dietary Supplement Health and Education Act and the Food and Drug Administration Modernization Act of 1997 (FDAMA). Under American guidelines, it is not mandatory that nutraceutical manufacturers seek approval with the FDA prior to commercialization, which means that some of these products can reach the market without proven clinical efficacy. This system has been criticized for potentially exposing consumers to unsafe and inefficacious products. From a business standpoint, this regulatory model reduces the time and financial expenses related to seeking approval prior to commercialization, significantly increasing the offer of nutraceuticals in the market (Lordan et al., 2021). In Canada, this segment is governed by Health Canada's Food and Drugs Authority, where nutraceuticals are rather viewed as pharmaceuticals than food. In this case, approval for health claims is conditioned to proven clinical efficacy in the form of *in vivo* studies conducted with human subjects. A similar regulatory approach is applied to Brazil, China, and Taiwan, although the nutraceutical concept is not well-defined, with such products being grouped as a food category in many instances. Also, when agri-food by-products are used as ingredients for developing nutraceuticals, an additional step may be required as some countries, such as Brazil and Canada, require their approval as new ingredients before they can be used in other applications (Santini et al., 2018).

6. Conclusions and future perspective

The transition from a linear to a circular economy in the agri-food industry holds immense potential for sustainability, economic growth, and the development of high-value products. The alarming statistics on global agri-food waste underscore the urgency of adopting circular practices. Agricultural by-products offer unique opportunities for creating value-added products such as functional foods and nutraceuticals. The pursuit of a zero-waste approach, where by-products are fully utilized, aligns with the principles of circular economy. However, challenges related to logistics, technology, bioefficiency, and regulation have been arresting the development of a more robust nutraceutical market segment despite of all of its economic potential. Addressing these challenges is pivotal for realizing the economic and environmental benefits of upcycling agri-food waste. The logistic challenges, from collection to transportation, necessitate innovative solutions and collaborative efforts among stakeholders. Technological hurdles in the extraction and preservation of bioactive compounds demand advancements, such as unconventional extraction methods and encapsulation approaches. Biological challenges highlight the need for enhancing the bioaccessibility and bioavailability of bioactive compounds serving as the basis for nutraceutical development. Regulatory frameworks, with variations globally, require harmonization to ensure the safety and efficacy of these products while also streamlining procedures required for their approval.

Despite these challenges, the potential rewards are substantial. Agri-food waste, when upcycled into nutraceuticals, could not only contribute to improved human health but also create new revenue streams. The burgeoning global nutraceutical market underscores the demand for health-promoting products. As we navigate the complexities of this ecosystem, the vision of a circular economy in the agri-food sector remains a beacon of sustainability and innovation. In this scenario, the importance of scientific research is vital. While preclinical research can clarify aspects related to the quality, efficacy, and mechanisms of action of novel nutraceuticals, clinical assessment can attest their safety and physiological benefits. This can pave the way for a new view on nutraceuticals, raising their status among consumers and health professionals as strong allies in preventive medicine. In the pursuit of this vision, interdisciplinary collaboration, research, and shared commitment are of paramount importance.

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