Natural Bioactive Compounds: Toxicity/Safety Concerns

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Although synthetic bioactive compounds are approved in many countries for food applications, they are becoming less and less welcome by consumers. Therefore, there has been an increasing interest in replacing these synthetic compounds by natural bioactive compounds. These natural compounds can be used as food additives to maintain the food quality, food safety and appeal, and as food supplements or nutraceuticals to correct nutritional deficiencies, maintain a suitable intake of nutrients, or to support physiological functions, respectively. Recent studies reveal that numerous food wastes, particularly fruit and vegetables byproducts, are a good source of bioactive compounds that can be extracted and reintroduced into the food chain as natural food additives or in food matrices for obtaining nutraceuticals and functional foods. This entry addresses general questions concerning the use of fruit and vegetables byproducts as new sources of natural bioactive compounds that are being addressed to foods as natural additives and supplements. Those bioactive compounds must follow the legal requirements and evaluations to assess the risks for human health and their toxicity must be considered before being launched into the market. To overcome the potential health risk while increasing the biological activity, stability and biodistribution of the supplements' technological alternatives have been studied such as encapsulation of bioactive compounds into micro or nanoparticles or nanoemulsions. This will allow enhancing the stability and release along the gastrointestinal tract in a controlled manner into the specific tissues. This review summarizes the valorization path that a bioactive compound recovered from an agro-food waste can face from the moment their potentialities are exhibited until it reaches the final consumer and the safety and toxicity challenges, they may overcome.

Keywords: bioactive compounds ; food waste ; toxicity ; nanotechnology ; regulation

1. Introduction

According to the Food and Agriculture Organization (FAO) one-third of the produced food is wasted [1]. The large amounts of agro-food waste represent a challenge for the food processors, but also an important issue for both environment and international economy since they are one of the causes for landfilling to be no longer sustainable [2][3]. Recent studies showed that agro-food wastes must be considered renewable source of added-value bioactive compounds (BCs) [4][5]. The current linear economy model is based on the one acquired concepts from the industrial revolution, which implied a constant supply of products with a short life span, forcing an ever so increasing production to face the consumers' needs [6]. This linear approach promotes the underexploitation of natural resources giving rise to a significant environmental and economic crisis. Contrarily, a circular economy encompasses the valorization of the waste allowing the extraction of novel ingredients by returning them to the supply chain, boosting the economy while reducing the environmental impact [3].

The majority of global food losses and waste (FLW) comes from the United States which covers approximately 40% of the whole food supply chain, followed by Central and East Asia and North Africa with 32%, European countries represents 20% while Latin America generates 6% of the FLW worldwide [7], which imply a significant impact on biodiversity, human health, and climate change. However, these FLW might be useful due to their high content of BCs in the production of food additives, functional foods, supplements, and nutraceuticals [5]. Hence, the proper management of this FLW will impact the change for a circular economy model and, a new concept perceived as an efficient option on the long run to transform and increment value to the FLW. BCs recovered from the food supply chain waste using sustainable extracting methodologies, will be used as raw material, or as new products, with health benefits creating industries with added value [6].

Current trends in the food industry and the continuous search for healthy products suggest that consumer's interest in natural and high-quality foods is increasing [8]. Moreover, the worldwide health crisis created by the COVID-19 redirected the current consumer attitude, perception, and behavioral patterns to reduction of food waste and also regarding the food products consumed [9]. Hence, attention to natural BCs has increased in the past year especially due to the consumers'

awareness regarding the evidence that a healthy and balanced diet has a positive impact on health therefore, consumers worldwide have become more health-conscious [10]. Furthermore, agro-food waste is a rich source of different BCs with content depending on the category of the waste, such as fruit and vegetables, dairy, meat and fish, cereals and roots, tubers and oilseed [3]. The FLW are cheap and renewable from which these BCs can be extracted to yield novel functional food products. Over the past few decades, the diversity of functional foods, supplements, and nutraceuticals in the global market is increasing. The global market of nutraceuticals, food antioxidants, and dietary supplements is expected to reach about $210 billion in 2026 [11]. Where Asia and North America are the main nutraceuticals and dietary supplements consumer markets in the world, whereas Europe focuses on collecting clinical evidence regarding the safety and health benefits of the functional products [12]. Overall, the interest of the food industry for more stable, functional, and user-friendly food additives that can be added to a high diversity of food products is increasing [13]. Because each country has specific laws, the legal aspects of natural BCs recovered from food waste used in a circular economy basis have to be defined. Global regulations and policies for the use of resources in a sustainable way must change from the usual processes (animal feeding, composting and anaerobic digestion) to the current ones (incorporation into the food industries) [6].

The reintroduction of recovered agro-food waste BCs faces many challenges including saftey, biological instability, potential contaminations (pathogens, toxins or pesticides) [14]. Because of that, those ingredients are considered as new foods that must undergo safety assessments likely to change according to different countries, yet limited, legislations concerning to the FLW utilization [15]. The stability and ingredients performance in a food system faces many challenges while designing the appropriate delivery systems for food additives, nutraceuticals, and dietary supplements [16]. The main objective of this review is to compile the journey of the BCs recovered from agro-food wastes until the final consumer, highlighting the safety and toxicity challenges that must be overcome.

2. Natural Bioactive Compounds

Bioactive compounds (BCs) definition is not consensual in the literature, however, one of the most well-accepted describes that they are “natural or synthetic compounds with the capacity to interact with one or more components in the living tissues and exerting a wide range of effects [17]. This term is not considered in regulations, however, because they can be part of food supplements, additives, nutraceuticals, functional foods, or novel food, the legal requirements consider them [13]. Furthermore, the boundaries between the food supplements, nutraceuticals, functional foods definitions are not clear and sometimes are confused [18]. Unlike dietary supplements and food additives, there are discrepancies and ambiguities in the definition of what nutraceuticals and functional food are, so a high overlap exists between the terms demonstrating wholesale uncertainty about what they are [19]. A deep analysis of the definitions and the inconsistencies found can be studied in a recent review work of Aronson [20]. Briefly, functional food contains certain substances that may be beneficial to the health in higher concentrations than that in conventional food. These compounds may contribute to enhancing the health benefits, being considered qualitatively more than conventional food [12]. The food additives are ingredients added during food processing for a technological function in order to ameliorate food quality and/or food shelf-life [5]. However, nowadays the interest in incorporating functional and natural food additives has gained significant impulse due to consumers becoming more aware of nutraceuticals and dietary supplements benefits in promoting health [13]. Similarly, the market growth of dietary supplements and nutraceuticals has been driven by consumer interest in health and well-being [21]. Nutraceuticals and food supplements are very similar terms, and they can assume several forms (tablet, capsule, etc.,). From the legal perspective, nutraceuticals represent a special part of dietary supplements because they contain ingredients used for preparing pharmaceuticals, but they do not need to pass through the same tests as pharmaceuticals [12][22].

The interest in BCs for food application in different ways continues to grow, powered by the ongoing research efforts to identify the health properties and potential applications of these substances, mainly extracted from natural sources, and coupled with public interest and consumer demand. They were commercialized as medicines because of their pharmacological assets and were mainly obtained from plants, vegetables, and fungi. The main challenge currently is using the non-edible parts of the natural matrices, such as FLW which still contains a high amount of different BCs with important benefits on human health to use for food industry.

Among the agro-food wastes fruits, vegetables, roots, tubers, and cereals together, have the highest wastage rates. The fruit production is dominated by citrus, watermelons, bananas, apples, grapes, and mangoes, while the most produced vegetables are tomatoes, onions, cucumbers and cabbages, and the roots and tubers are carrots and potatoes [23]. Bioactive compounds isolated include mainly polyphenols, tannins, flavonoids, flavanols, vitamins (A and E), essential minerals, fatty acids, volatiles, anthocyanins, and pigments [24]. By-products from the animal industries represent a good source of bioactive peptides and proteins. Those may include derived products from meat and fish (with side streams

bones, tendons, skin, parts of the gastrointestinal tract and other internal organs, and blood) [25]. The dairy industry is another valuable source of proteins and peptides, specially from cheese production [26].

Another alternative presented nowadays for large volumes of produced wastes is the production of energy through the use of biomass or as animal feed (**Figure 1**). Nonetheless, the wastes are still rich in other valuable compounds such as pigments, sugars, organic acids, flavors, phytochemicals, enzymes, antimicrobial compounds, and fibers that could be extracted in order to use as food additive or supplement with higher added value [27]. Furthermore, the recovery of these BCs is a challenging and important task for their return to industrial chains (commercialization) applying the circular economy concept in order to be employed for the arising trends regarding human demand [3].

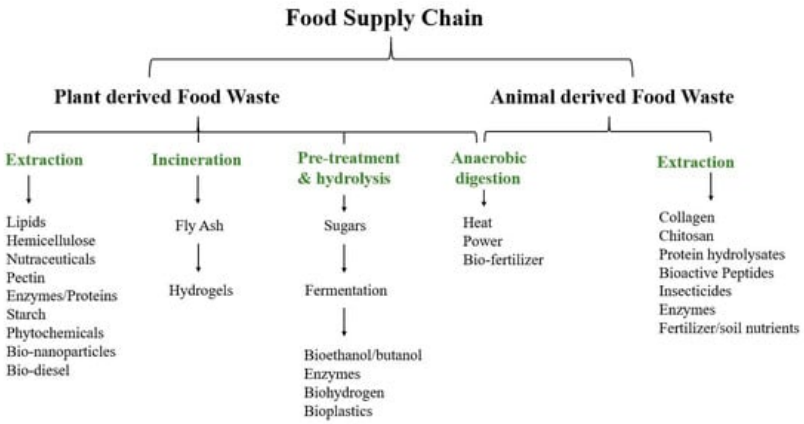

Figure 1. Possible new bioactive compounds extracted from agro-food waste.

Several extraction methodologies have been reported for the recovery of bioactive compounds from agro-food wastes that use organic solvents however, there is a growing need for green and sustainable alternatives. The green extraction technologies that have been the focus are the microwave-assisted extraction (MAE), ultrasound-assisted extractions (UAE), and supercritical fluid extraction (SFE) [4]. Recently the use of natural deep eutectic solvents for the bioactive compounds recovery received great attention as an alternative to the conventional extraction which uses organic solvents that may contribute to toxicity, presenting high volatility and non-renewability [28].

Extensive research in the past few years intends to demonstrate the value of FLWas a resource of compounds with bioactivity or technological potential to introduce new, more sustainable, and natural alternatives to the market. The consumer's preferences for "clean labels" determines the use of natural compounds to replace synthetic ones, motivating the scientific community to search for new sources of natural alternatives, directing their attention to the utilization of agro-food by-products [5]. One of the most reported potential was the fruit and vegetable waste, since it generates a high amount of residue in the food supply chain and is rich in different types of compounds that can be used for different purposes [3].

2.1. Antioxidants

Currently, there are a lot of antioxidant compounds which are already being used in the food industry, mainly as a food additive, and are permitted by regulations, such as ascorbic acid, α-tocopherol, rosemary extract [29]. However, the main challenge nowadays is recovering compounds with the same potential from waste and proving their safety and functionality for introduction in the food system [30]. Any by-product can be considered a valuable resource of new antioxidant food additives, e.g., overly ripe berries, non-compliant fruit, peels, pomace, and seeds. A recent study from Muíno et al. [31] described the use of an olive oil waste extract rich in polyphenols as a potential natural antioxidant applied to lamb meat patties, delaying the lipid and protein oxidation while maintaining acceptable color for a prolonged time, extending the product shelf-life to 3 days. Another recent work from Bitalebi et al. [32] observed that apple peel extract (APE) inhibited protein and lipid oxidation in rainbow trout *Oncorhynchus mykiss* mince during refrigerated storage (4 °C). Furthermore, lipid oxidation was inhibited (96 h at 4 °C) lowering the peroxides and thiobarbituric acid-reactive substances (TBARS) when compared to control.

2.2. Preservatives

The most common preservatives in the food industry are nitrates (E240-E259) and nitrites (E249-E250) and they are related to the development of carcinogenic compounds responsible for developing cancer [5]. Therefore, natural antimicrobials that can be added to food are mainly terpenes, peptides, polysaccharides, and phenolic compounds, among others with less expression. The agro-food byproducts are a major source of these compounds with several

reports showing the potential antimicrobial activity of different BCs. For instance, olive leaf extract was used to reduce bacteria contamination in shrimp and organic leafy greens [33][34]. Meat products quality and shelf-life was increased [35] and the capacity to delay fish microbiological spoilage (*E. coli, L. monocytogenes* and *S. aureus*) resulted in extending fish shelf-life under retail conditions [36]. Moreover, the antimicrobial capacity of pomegranate peel extract were investigated in chicken products [37][38] and, the extract showed good antimicrobial activity against *S. aureus* and *B. cereus*. In general, addition of pomegranate peel extract to popular chicken and meat products enhanced its shelf-life by 2–3 weeks, during chilling temperature [39].

2.3. Anti-Browning

The resulted decrease in fresh produce quality and shelf-life results from enzymatic browning [40] and consequently negatively impacts product color, taste, flavor, and nutritional value. One solution presented to reduce this phenomenon is using antioxidant solutions and two of the most effective and traditionally used solutions are the ascorbic acid, its derivatives, and sulfites [8]. The use of natural compounds with anti-browning properties would be of unquestionable importance for better consumer acceptance of these products. Compounds with a strong antioxidant capacity such as phenolic compounds have been presented as potential inhibitors of oxidative enzymes. This was demonstrated by a recent work developed by Cindy Dias et al. [40] that uses extracts from strawberry tree (leaves and branches) and apple byproducts to inhibit polyphenol oxidase and peroxidase.

2.4. Colorants

Most available commercial colorants are synthetics however, a few of them like carotenoids and anthocyanins are already obtained from natural sources [5]. Therefore, the use of FLW as new source of colorants could be a way to shift to more natural additives in the food industry, while still maintaining a cost-effective production. The 16 natural pigments permitted in EU were specified in the Regulation (EC) No. 1333/2008. Good examples of natural color additives are the anthocyanins and carotenoids since in nature they are responsible for the blue, red, purple, orange, and yellow coloration of several species in the plant kingdom. Some examples of anthocyanins sources are winery byproducts, red cabbage, black carrots, purple sweet potatoes, and berries [41]. Blackberry residues are one of the most important sources of natural colorants and nutraceuticals (4.31 mg Cy3GlE/g) [42]. Citrus peels and pomace residues are good sources of carotenoids [43][44]. These compounds can be used for natural colors in products, and beyond that enhancing the shelf-life of food and beverages by preventing pathogens and contaminants or off-flavor formation.

2.5. Thickeners

Citrus peels are also rich in pectin. Therefore, pectin extracted from citrus peels could be applied as a gelling agent in bakery, confectionery, and in meat products. Water-insoluble fibers as pectin are also considered a functional food that are used to improve gut microbiota health [29][43].

3. Food Waste Bioactive Compounds Regulatory and Legislative Issues

The interest in food industry toward development of functional and nutraceutical products is increasing and the BCs extracted from FLW can be re-used in the human food supply chain as nutraceuticals, functional foods [44], additives, supplements, fortification, and other minor ingredients [14]. One of the challenges related with FLW valorization is the lack of effective policy and is growing the necessity to improve the statutory rules, codes of conduct and guidelines. The utilization of BCs recovered from FLWare still limited to scientific research and patents, because there is still a lack of legislation for FLW utilization [15].

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