CHAPTER

Opportunities and challenges of plant extracts in food industry

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13.1 Introduction

Plant extracts derived from different parts of the plant are used for various food applications because of their preservative, aromatic, antimicrobial, and medicinal properties. Plant extracts are obtained from different sources and parts of the plant such as leaf, fruit, seed, bark, peel, stem, root, and flower. The crude extracts from plants are still in use in folk medicine and traditional systems of therapy, as well as food supplements. Modern techniques of isolation, purification, and incorporation enhance the use of plant extracts in the food industry.

Research over the last two decades points to reduced risk of several chronic diseases such as diabetes, cancer, and cardiovascular diseases due to the regular consumption of many plant extracts (Liu, 2004; Mir, Shah, Ganai, Ahmad, & Gani, 2019). The demand for phytomedicines and herbal extracts is increasing significantly in various applications, including functional foods, nutraceuticals, and health care, due to the growing awareness of their health benefits among consumers. Many studies corroborate this and indicate a high growth in this sector both in developed and developing nations. Given this scenario, the opportunities of plant extracts to be used in foods applications are increasing rapidly. However, there are several challenges, especially with respect to their stability, efficacy, and formulation during production. Furthermore, the interaction of plant extracts with other components of the food matrix and bioavailability along with required standards and regulations are also the challenging factors.

13.2 Opportunities

13.2.1 Prebiotics

Prebiotics are nondigestible and selectively fermentable ingredients that allow specific changes in the composition and/or activity of the gastrointestinal microbiota to confer benefits upon host health and well being (Gibson, Probert, Rastall, & Roberfroid, 2004). They are largely

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plant-derived components, which are widely used in bakery products, sports drinks, sugar-free confectionery, fermented milks and yogurts, baby foods, and chewing gum (Azmi, Mustafa, Hashim, & Manap, 2012). Prebiotics comprise of short-chain carbohydrates, mainly oligosaccharides, for example, fructooligosaccharides (FOS), xylooligosaccharides, galactooligosaccharides (GOS), human milk oligosaccharides (HMO) and polysaccharides like inulin (Panitantum, 2004). Prebiotics occur naturally in fruits and vegetables and small amounts are found in the form of free sugars or glycoconjugates in human milk and animal colostrums (Bucke & Rastall, 1990). However, compounds with prebiotic properties are not limited to pure carbohydrates and fibers but are also expanded to polyphenols.

Polyphenols are secondary plant metabolites that represent a large group of 8000 different compounds. They are structurally made up of one or more aromatic rings attached to one or more hydroxyl groups (González-Centeno et al., 2013). Polyphenols are abundantly found in fruits, vegetables, cereals, nuts, spices and herbs; the common among them are flavonoids and phenolic acids (Araújo, Gonçalves, & Martel, 2011). Dietary polyphenols are mostly found in glycosylated forms with sugar residues conjugated to a hydroxyl group or the aromatic ring. While their absorption is low, they are metabolized in the colon by the colonic microflora (Mocanu, Nagy, & Szöllosi, 2015).

The crude extracts obtained from several plant materials with rich source of phenolic compounds have potential application as preservatives and are also used in the development of several functional foods and nutraceuticals. Prebiotics can sustain high processing temperatures and are stable under low pH conditions making their use in foods highly feasible. Prebiotic fibers, oligosaccharides and polyphenols are incorporated in bakery foods, cereals, beverages, dairy products, and food supplements.

Among the prebiotics, the functional oligosaccharides like FOS, GOS, XOS, IMO, and HMO produced as purified compounds from their respective carbohydrate substrates have multiple food applications such as sugar replacers, fat replacers, and prebiotic and weaning foods (Singla & Chakkaravarthi, 2017). With respect to polyphenols as prebiotic agents, research has been carried out largely with crude extracts from olive pomace, grape seed extract, walnut husk, pomegranate peel, red chicory by products and various other sources. Novel prebiotics and their effects on rheological, textural, sensorial and nutritional profiling of nutraceuticals need to be studied for their usage in the food industry. Prebiotics may find interesting applications as energy bars and meal replacement shakes to increase the health component associated with them (Spacova et al., 2020).

Single compounds such as catechin, epigallocatechins, resveratrol, rosamarinic acid, and anthocyanins have also been studied in various foods for their physiochemical benefits (Xie, VanAlstyne, Uhlir, & Yang, 2017). There is evidence that crude plant extracts often have greater pronounced in vitro or/and in vivo prebiotic activity due to synergistic effects than the isolated constituents at an equivalent dose (Rasoanaivo, Wright, Willcox, & Gilbert, 2011). The activity depends on a number of factors: the polarity of the solvent used for extract and solubility of the targeted bioactive (Chemat et al., 2020).

13.2.2 Herbs

The demand for phytomedicines and herbal extracts are gaining tremendous popularity among the consumers due to their immense health benefits and the preference for the use of natural products rather than the synthetic ones. They are widely used in functional foods, health care, nutraceuticals, skincare, and cosmetics (Oreopoulou, Tsimogiannis & Oreopoulou, 2019). The leaves of many plants, including aloe vera, rosemary, basil, thyme, clove leaves are rich in antioxidants and also offer antimicrobial properties; which has led to their extensive application (Oreopoulou, Tsimogiannis & Oreopoulou, 2019).

13.2.2.1 Herbal polyphenols

Aromatic and medicinal herbs are rich sources of polyphenols; rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), winter savory (*Satureja thymbra*) oregano (*Origanum vulgare ssp. hirtum*), and marjoram (*Majorana syriaca*) are among the most promising sources of polyphenols (Oreopoulou, Tsimogiannis & Oreopoulou, 2019). All of these herbs belong to the *Lamiaceae* family and are used as spices or for the recovery of essential oils through the process of hydrodistillation. The use of spices and essential oils in active packaging of processed food has seen a rising trend in food technology (Fernández-López & Martos, 2018). Green tea has been considered as a good source of polyphenolic compounds; catechins (also known as flavanols), including catechin gallate, epicatechin, epigallocatechin, epicatechin-gallate, epigallocatechin-gallate, gallocatechin gallate, and gallocatechin are the dominant phenolic compounds that have varied food applications (Musial, Kuban-Jankowska, & Gorska-Ponikowska, 2020). Basil extracts containing high contents of Vitamin A, Vitamin K, Vitamin C, iron, magnesium, potassium, and calcium are used extensively in food and beverage applications (Fernández-López & Martos, 2018).

The dried herbs or the residues after essential oil recovery, currently disposed as waste, could be utilized to obtain natural extracts rich in phenolic compounds and with high antioxidant activity. Even though essential oils are promising alternatives to chemical preservatives, they have special limitations, such as low water solubility, high volatility, and strong odor, which must be addressed before application in food systems. (Fernández-López & Martos, 2018).

13.2.2.2 Herbal alkaloids

Alkaloids are a vast group of naturally occurring secondary metabolites synthesized by plants and animals. They are derived from amino acids and contain a nitrogen atom or atoms (amino or amido in some cases) in their structures, the reason behind the alkalinity of these compounds (Aniszewski, 2015). They are generally the main bioactive component of the plant that is isolated naturally or sometimes synthesized for their applications in the food and pharma industries. Many alkaloids are found as elements of the human diet such as coffee seeds (caffeine), tea leaves (theophylline, caffeine), cacao seeds (theobromine and caffeine), tomatoes (tomatine), and potatoes (solanine) (Aniszewski, 2015). Caffeine is the most common alkaloid having application as an ingredient of soft drinks like Coca-Cola to enhance their taste and in sport drinks. Some alkaloids are components of modern food and spice mixes. The black, green, white pepper (*Piper nigrum* L.), and long peppers (*Piper longum L.*) contains piperine that is widely used in food. Capsicum peppers such as Peruvian pepper (*Capsicum baccatum L.*), chili or red pepper (*Capsicum annuum L.*), bird pepper or tabasco (*Capsicum frutescens L.*), ají pepper (*Capsicum chinese Jacq.*), and rocoto pepper (*Capsicum pubescens Ruiz et Pav.*) have a wide range of food applications in food packaging and preservation (Aniszewski, 2015). Quinine is a well-known alkaloid with no color and a bitter taste; whose bio-activity is used in food as additional supplement to the refreshment drinks with water, sugar, carbon dioxide, and protectors E 320 and E 211 (Aniszewski, 2015). More common alkaloids are pyrrolizidine, quinolizidine, beta-carboline, ergot, and steroid alkaloids. Some alkaloids such as piperine, nicotine, theobromine, and tropane have low or negligible risk in the normal food chain. However, their use outside the normal food chain, in pure doses is not safe and reasonable only in clinical practice (Aniszewski, 2015). Scientists still keep trying to design and synthetize more and more semisynthetic and synthetic alkaloids derived from natural sources of alkaloids.

There are many more herbs used by local communities and ethnic groups in South American, Middle Eastern, Asian, African, and Oceania countries, which are used at domestic or community level, but not studied in depth. The scope for leveraging such plant sources to benefit producers and consumers is still large.

13.2.3 Spices

Spices are parts of plants used as colorants, preservatives, or medicine, due to their functional properties and many have a long history of use. Spices are known for culinary application as seasoning ingredients in various cultures, for example, garlic, onion, cinnamon, anise, clove, and red pepper are preferred seasoning agents of Chinese culture while coriander and black pepper are likely consumed in the East Indian region (Opara & Chohan, 2014).

The wider classification of spices come from *Monocotyledoneae* plants, such as garlic, ginger, turmeric and vanilla or from *Dicotyledoneae* plants, such as paprika, pepper, nutmeg, cinnamon, and clove (Chhetri et al., 2018). Spices are derived from bark, fruit, seeds, or leaves of plants and often contain spice-specific phytochemicals. Polyphenols are the major chemical compounds that are present in herbs and spices, which, especially in their dried forms, generally contain relatively high levels of polyphenols compared to other polyphenol rich foods including broccoli, dark chocolate, red, blue and purple berries, grape and onion (Pérez-Jiménez, Neveu, Vos, & Scalbert, 2010). Different spices such as clove bud, turmeric, celery, parsley, mint, rosemary, thyme, sage, dill, curry and ginger contain high levels of polyphenols (Mocanu et al., 2015).

13.2.3.1 Spice-based polyphenols and oleoresins

The application of spices as natural colorants is highly recommended against the chemical or synthetic forms. The spices tint in different colors from yellow and orange to different variations of red (except chlorophyll from herbs). Commonly used spices for coloring are red pepper, paprika, ginger, mustard, parsley and turmeric. The coloring property of spices is due to the lutein and neoxanthin and carotenoids, such as β carotene (Bartley & Scolnik, 1995). Other compounds that provide these coloring properties are flavonoids with yellow colors, curcumin with orange and chlorophyll with green (Peter & Shylaja, 2012). There are reports in literature on processing of spice spent residues into value-added products, viz. preparation of bakery products, snacks, and bio-films. Essential oils and spice extracts have been widely explored for shelf stability of shallow and deep-fried meat, raw and processed chicken, dried cured meat, fermented meat and meat sausages (Lu, Kuhnle, & Cheng, 2018). The application of some spices as preservatives in food has been evaluated to determine their efficiency, since spices are natural sources and offer an opportunity to replace synthetic preservatives in food, such as nitrates, which have been claimed to possess negative effects on human health (Anand & Sati, 2013). Some of the chief chemical compounds in spices are eugenol in clove, cinammaldehyde in cinnamon, cuminaldehyde in cumin, and curcumin in turmeric which have been proven to prevent food spoilage and inhibit the growth of pathogenic microorganisms. They are best known for their strong antioxidant properties that exceed the levels in most foods.

Spice oil is a spice derivative, a secondary metabolite of spices with spice flavor and fragrance properties that is extracted generally by steam distillation process (Singhal & Kulkarni, 2003). The various food applications of spice oils include beverages, cosmetics, perfumery and toiletries. Spice oleoresins are the concentrated liquid form obtained from spices with same character and properties of spices. Oleoresins are commonly used as food flavorings, liquid seasonings for improving the flavor, aroma and taste profile in foods by processing industries (Singhal & Kulkarni, 2003). They have many applications as a coloring agent in butter, cheese, meats, snack foods, and cereals; in frozen foods, soups, desserts, meat sauces, fish preserved in oil, or any prepared food where a more vibrant color is desired; in jellies, jams, and preparation of gelatin. Oleoresins are typically dispersed in a dry neutral carrier or liquid such as vegetable oil to the desired strength. About 80%–90% of spices left over as spent residue in the spice oil and oleoresin industries are not commercially exploited for food application and provide ample scope for investigation to identify bioactive that can find suitable applications in foods (Singhal & Kulkarni, 2003).

13.2.4 Whole extracts versus purified components

Pure or isolated drugs that are industrially produced may be chosen for their high activity against human disease; however, they have their own disadvantages. They hardly have the same degree of activity as the crude extract at comparable concentrations or dose of the active component (Wagner & Ulrich-Merzenich, 2009). This could be attributed to the absence of interacting co substances present in the extract.

The crude compounds showing increased activity relates to the evidence of synergy that several mechanisms may be operating in parallel, although the exact mechanisms have not yet been delineated. In pharmacodynamic synergy, various substances act at different receptor targets involved in the disease to improve the overall therapeutic effect. The substances with diminutive or no activity on the causative agent, support the main active principle to reach the target by improving its bioavailability, or by decreasing the metabolism and excretion.

13.2.4.1 Herbs and spices

Synergy between the different constituents of the crude extract has been reported for many pharmacological activities (Houghton, 2009). Curcumin, the bioactive compound from turmeric, that is, *Curcuma longa* root and the whole turmeric itself is reported to have traditional remedies for malaria and fever (Mishra, Dash, Swain, & Dey, 2009). When used in combination with artemisinin (derived from *Qinghao*, a plant called sweet wormwood), curcumin prevents the recrudescence of malarial parasites and death in animal models (Mishra et al., 2009).

However, when used in combination with *Andrographis paniculata* and *Hedyotis corymbosa* extracts, curcumin exhibited a clear synergistic effect in vitro *and* in vivo in rodent malaria models (Mishra et al., 2009). Curcumin alone has shown to have poor oral bioavailability due to glucuronidation in the small intestine, but piperine from black pepper (*P. nigrum* seeds) enhanced the bioavailability of curcumin by 2000% in humans, by inhibiting glucuronidation and slowing the gastrointestinal transit (Shoba et al., 1998). Piperine has also shown to improve the bioavailability of epigallocatechin-gallate (EGCG) which might improve its activity as a multidrug resistance inhibitor in vivo (Rasoanaivo et al., 2011).

There are several reports of synergy between the extracts of different plants, which are traditionally combined, but the mechanisms of the synergy have not yet been clarified (Rasoanaivo et al., 2011). More clinical trials of combinations of pure compounds (such as piperine + artemisinin + curcumin) and of combinations of crude extracts (such as *C. longa* root + *Artemisia annua* leaves + *Piper nigum* seeds) is fundamental to understand the interaction between plant constituents. Such research focus can enhance the activity of existing pharmaceutical preparations as well as improve the effectiveness of the existing herbal remedies for use in food and modern drug applications (Rasoanaivo et al., 2011).

Till date, the exploitation of spices for the recovery of polyphenols and their applications as antioxidants in food systems, food supplements, or cosmetics has been very scarce. Considering spices, the decoction or extracted crude compounds are mostly used. However, few isolated compounds like rosmarinic acid, several essential oils from thyme, savory, marjoram, cinnamon, oregano and garlic are used as additives in biodegradable films and coatings for active food packaging applications (Fernández-López & Martos, 2018).

13.2.4.2 Prebiotics—nondigestible oligosaccharides (fructooligosaccharides, galactooligosaccharides, and xylooligosaccharides)

Fractionation and purification procedures are mandatory for oligosaccharide, as the elimination of mono- and disaccharides fractions is required to evaluate and enhance their functional properties (e.g., in vitro prebiotic activity). Purification also helps in gaining enriched bioactive fractions for their use as food ingredients in specialized products (for individuals with disorders like diabetes, lactose intolerance, etc.), and in low calorie foods with a reduction of mono- and disaccharides. The most commonly used purification steps are filtration, centrifugation and precipitation. The purification of functional oligosaccharides based on adsorption techniques using various adsorbents such as: aluminum hydroxide or oxide, activated carbon, bentonite, silica, titanium and porous synthetic materials have been stated in literature (Qing, Li, Kumar, & Wyman, 2013).

However, despite its promise for industrial-scale purification and concentration of oligosaccharide mixtures, fractionation of oligosaccharide mixtures is still a challenge. Selective fermentation (bioconversion) can be a plausible technological alternative for purification of GOS using yeast strains from the genera *Saccharomyces* and *Kluyveromyces* (Guerrero et al., 2014). The basis of this strategy is the selective removal of the metabolizable sugars (monosaccharides plus lactose, or monosaccharides only) from raw GOS by yeast fermentation (bioconversion).

The above-mentioned techniques present advantages and disadvantages that must be taken into consideration in the design during the purification at an industrial scale. Although, effective removal of monosaccharides is a necessary step, still it will require an enzymatic pre-hydrolysis step with the consequent reduction in productivity and increase in cost. A financial evaluation of these strategies in commercial production will throw light as to their real industrial potential.

13.2.4.3 Polyphenols—quercitin, catechin, epigallocatechin, curcumin, capcisin, and allicin

To obtain a high-quality extract for its suitable use in the food, cosmetic, and pharmaceutical industries, the extract must be purified to remove all inert and undesirable components. Purification improves the functional properties of plant extracts and minimizes any taste, odor, and color (Peschel et al., 2006). It has been observed that the purified secondary metabolites are usually more active than the crude extracts, on condition that, there is no synergism within the mixture, so that it gets suppressed when molecular entities are separated and purified (Peschel et al., 2006).

To obtain a single or pure fraction of polyphenolic compounds, it is necessary that an effective purification step should be carried out after extraction to remove the impurities. The purification of active component depends on the structure, stability, and quantity of the compound. There are different approaches used to purify polyphenolic crude extract after extraction. The common technique is organic solvent extraction, followed by evaporation and reconstitution with distilled water. Solid phase extraction on columns such as Sephadex LH-20, Diaion HP-20, or C-18 are used extensively for purification (Suwal & Marciniak, 2018). Polyphenols can also be recovered with methanol or aqueous acetonitrile when using C-18 cartridges (Suwal & Marciniak, 2018).

The method of chromatographic fingerprinting using reverse-phase high-performance liquid chromatography helps in metabolite profiling of crude extracts. The highly complex vegetable matrix requires a high-resolution metabolite profiling as well as rapid fingerprinting of crude plant extracts which can be achieved by ultra-high-pressure liquid chromatography (UHPLC). UHPLC allows higher separation efficiency and resolution, increases the speed of analysis, lower solvent consumption and high sensitivity. With the use of HPLC micro-fractionation, the constituents can be fractionated and collected into 96 well microplates for further biological screening. The action observed in the microplate wells can be directly corresponded to the component in the chromatogram, which allows rapid localization and further scale-up purification (Grosso, Jäger, & Staerk, 2013).

A successful and simple method such as semipreparative high-performance liquid chromatography was carried out to purify tea catechins: catechin (C), epicatechin (EC), gallocatechin (GC), epigallocatechin (EGC), epigallocatechin-3-O-gallate (EGCG), epicatechin-3-O-gallate (ECG), and epigallocatechin-3-O-(3-O-methyl)-gallate (EGCG3"Me) (Gong et al., 2017). Literature have also shown that a high recovery efficiency of EGCG can be obtained by using cyclic ion exchange chromatography (IEC) techniques. The process uses minimal solvents (30% ethanol) as compared to conventional techniques (Acikara, 2013). Polyphenols such as epigallocatechin-gallate (EGCG), epicatechin-gallate (ECG), and epigallocatechin (EGC) were separated by using weakly acidic cation exchange gels (dextran based) from crude tea extracts without using any solvent (Banerjee & Chatterjee, 2015). Thin layer chromatography was observed as a simple, economical and efficient technique to isolate and purify spices such as curcuminoids, allicin, capsascin, and cinnamldehydes (Pawar, Gavasane, & Choudhary, 2018).

In this fast-growing field of bioactives from plant extracts, the opportunities are wide, with scope for utilization, once the scientific understanding is fairly comprehensive and due consideration is given to challenges arising.

13.3 Challenges

13.3.1 Food versus supplements

Functional foods (also referred to as foods for special dietary use/health supplements/nutraceuticals/similar such foods) should be distinguished from conventional foods, and therefore such products may be formulated as capsules, granules, jellies, liquids, powders, tablets, and other dosage forms, which are meant for oral administration (FSSAI – Food Safety & Standard Act, 2006).

According to different studies, the use of food supplements is mainly associated with being female, high education level, high household income, older age, and use of over-the-counter drugs (Timbo, Ross, McCarthy, & Lin, 2006). Despitethis, the consumers are now generally aware and careful about their health status and the growing use of botanicals has been associated with a possible risk of adverse effects, taking also into consideration the thousands of plant food supplements (PFS) present in the market. Although the incidence of mild to severe adverse effects is generally low (about 4% according to European and US data from surveys among consumers) and some plants have been traditionally used from thousands of years, many of them have not been tested in scientific studies and their efficacy and safety not established sufficiently (Lüde et al., 2016).

Functionality through randomized controlled trials (RCTs) in normal healthy and individuals with disease throws light on the use of plant extracts for specific purposes. Studies by Onakpoya, Davies, Posadzki, and Ernst (2013) and Lee, Chung, Fu, Choi, and Lee (2020) focused on (1) healthy individuals (less than 20% had cardiovascular disease/diabetes/people who were obese); (2) oral intake of IGOB131, a proprietary patented form of *Irvingia gabonensis* seed extract, or any other preparation of *I. gabonensis* seed extract; (3) outcomes related to weight (body weight, body fat, and waist circumference), cardiovascular biomarkers (high-density lipoproteins, low-density lipoproteins, total cholesterol, triglycerides, and blood pressure); and (4) parallel or crossover RCTs. RCTs of *I. gabonensis* seed extract supplementation on anthropometric measures and cardiovascular biomarkers were identified from 4 databases by Lee et al. (2020). Among 5 RCTs, 4 were rated with high risk of bias (ROB) assessment, and only 1 with low ROB. Random-effect *meta*-analysis of the 5 RCTs showed decrease in body weight, body fat, and waist circumference to *I. gabonensis* seed extract supplementation. However, RCT with low ROB did not have significantly different outcomes. Overall efficacy of *I. gabonensis* seed extract supplementation on weight loss seemed positive but was limited due to poor methodological quality and insufficient reporting of clinical trials. Further, high-quality RCTs are needed to determine the effectiveness of *I. gabonensis* seed extract supplement on weight-related health outcomes. A 2013 systematic review identified only 3 RCTs and concluded that *I. gabonensis* cannot be recommended for weight loss (Onakpoya et al., 2013).

Critchley, Zhang, Suthisisang, Chan, and Tomlinson (2000) suggested that the controls should be carefully chosen such that they closely match with the intervention group as well as standardized for factors such as color, odor, duration, and frequency of intake. Nevertheless, in certain natural products such as ginger, which has a peculiar odor, choosing a matching control is an uphill task. The few randomized, double-blind tests that attracted attention in mainstream publications were often questioned based on methodological grounds or interpretation in terms of reproducible results (Pittler, Abbot, Harkness, & Ernst, 2000). Jiménez, Delgado, and Muguerza (2004) reported that intake of Funciona (330 mL/day), a blend of antioxidant-rich fruit extracts enriched with antioxidant vitamins reduced oxidative stress in elderly people. Antioxidant supplementation showed optimum level of defense against the free radical generation associated with aging and exercise in 400 healthy aged (58–86 years) subjects on moderately intense exercise (50 min sessions, 3 sessions/week).

Camellia sinensis (green tea) has been associated with hepatotoxic effects mainly due to the intake of high amounts of epigallocatechin-3-gallate (EGCG). This effect is also mediated by the type of extraction used: hydroalcoholic extracts were more involved in adverse effects (Di Lorenzo et al., 2015).

13.3.2 Stability

Given the current trend of health promotion through diet, understanding the processing effects is critical for conserving active phytochemicals. Phytochemicals present in most foods are lost by heat processing such as dehydration, pasteurization, and sterilization. Thermal processing caused marked losses in total anthocyanins in blackberries (Hager, Howard, Liyanage, Lay, & Prior, 2008) and blueberries (Brownmiller, Howard, & Prior, 2008). It also decreased the biological activity of drumstick leaves extract (Arabshahi, Devi, & Urooj, 2007). However, no difference in activity of carrot tuber extracts was observed before and after heat treatment, while in some cases, processing induced the formation of novel compounds that either maintained or even increased the potential of various fruit and vegetable extracts (Nicoli, Anese, & Parpinel, 1999).

During thermal processing of food, total phenolic contents decreased by 20.21% on heating at 70°C for 30 min. Catechin was stable at room temperature, but on brewing at 98°C for 7 h, it degraded by 20% (Chen, Zhu, Tsang, & Huang, 2001). The degradation of gallic acid was 15% at 80°C after 4 h of exposure (Volf, Ignat, Neamtu, & Popa, 2014). Drying temperatures of 100 and 140°C reduced the total polyphenol content of red grape pomace peels by 18.6% and 32.6%, respectively (Larrauri, Rupérez, & Saura-Calixto, 1997). Storage conditions directly affected the polyphenol content due to hydrolysis, oxidation, and complexation (Zafrilla et al., 2003). At 18°C, 28°C, and 38°C, hydrocinnamic acid of orange juice decreased by 13%, 22%, and 32%, respectively after 6 months of storage (Klimczak, Małecka, Szlachta, & Gliszczyńska-Świgło, 2007). At 4°C, polyphenols were stable for longer periods, which was attributed to the inhibition of phenol oxidases at low temperature (Wei & Ying-tuan, 2008).

Significant changes in individual isoflavone levels were observed during the storage of ultra-high temperature processed chocolate flavored high protein beverage containing soy protein isolates depending on storage temperatures (4°C, 23°C, and 38°C), but total isoflavones remained the same irrespective of storage temperature or duration (Hayes, Unklesbay, & Grun, 2004). Hexane extract from *Garcinia* was more suitable in biscuit preparation than turmeric powder, as it retained high antioxidant activity after baking, followed by 2 months of storage (Nandita et al., 2009). Flower extracts of *Peltophorum ferrugineum* (Nanditha, Jena & Prabhasankar, 2009); and marjoram, spearmint, peppermint, and basil powders or their purified extracts (Bassiouny, Hassanien, Ali, & El-Kayati, 1990) were also found to retain their antioxidant activity during baking process. Biscuits with extracts of raisins, amla, and drumstick leaves were stable during 6 weeks of storage (Reddy, Urooj, & Kumar, 2005).

Ingredient formulators use spray-drying method to convert liquids into easy-to-handle powders and release of polyphenols without affecting their functional properties (Sansone et al., 2011). Maltodextrins are the commonly used coating material, especially for anthocyanins from sources such as apple pomace. However, inlet air temperature above 160°C–180°C can cause loss of anthocyanins (Tonon, Brabet, & Hubinger, 2010). Microwave-assisted extraction (MAE) is an advanced, efficient, and rapid method for extracting phenolic compounds. Extraction rate of flavonoids in pomegranate slag increased with increase in extraction time, which was highest at 6 min (Cai & Zhang, 2012). MAE can prevent the degradation of polyphenols due to the shorter extraction time.

In general, when pH value is lower, the stability of polyphenols will be greater. According to Chethan and Malleshi (2007), the phenolic contents in the millet seed coat extract remained constant at highly acidic to nearly neutral pH (6.5) but decreased as the alkalinity increased to pH 10. Tea catechins in aqueous solutions were stable at pH $<$ 4 and unstable at pH $>$ 6 (Ananingsih, Sharma, & Zhou, 2013), while *Galla chinensis* extracts with substantial amounts of tannins were unstable at neutral and alkaline conditions (Huang et al., 2012). In acidic aqueous solutions, anthocyanins exist in equilibrium as four main species namely, flavylium cation, quinonoidal base, pseudobase, and chalcone. At pH 1, flavylium cation (red color) is predominant. As pH increases, due to loss of proton, the quinonoidal base is formed. Between pH 5 and 6, pseudobase and chalcone are observed. At pH $>$ 6, anthocyanins are degraded (Castañeda-Ovando, de Lourdes Pacheco-Hernández, Páez-Hernández, Rodríguez, & Galán-Vidal, 2009).

Duration and magnitude of high-pressure processing (HPP) have strong influence on polyphenols' stability. The polyphenols content did not change in pressure-treated strawberry puree although the total anthocyanins decreased (Marszałek, Mitek, & Skąpska, 2015). Cyanidin-3-O-glucoside (Cy3gl) subjected to HPP at 600 MPa and temperature of 70°C with longer holding time (6 h) reduced by 35% due to condensation of (Cy3gl) with pyruvic acid by formation of a new pyran ring by cycloaddition (Corrales, Butz, & Tauscher, 2008). Although HPP has a negative effect on stability, content, and antioxidant activity of polyphenols, it was slighter compared to thermal processing.

13.3.3 Interactions

A comprehensive understanding of the interaction between proteins and phenolic compounds as well as their characteristics is essential to develop the novel conjugates with improved functional and bioactive properties for better applications in food or related systems.

Basically, proteins and polyphenols can interact together via either noncovalent (hydrophobic, ionic, and hydrogen bonding) or covalent bonds (You, Luo, & Wu, 2014). However, the conjugates formed by covalent bonds are more preferably used in food applications owing to their stronger and more permanent interactions with high stability (Liu, Ma, Gao & McClements, 2017). Noncovalent protein–polyphenol interactions generally result from a combination of different interactions. Even though the bonds formed are potentially reversible and have low energy, the noncovalent protein–polyphenol interactions may play an important role in food industries for improvement of functional and quality of food products (Liu et al., 2017).

There are two main factors affecting the interaction between proteins and polyphenols. Those include extrinsic (pH and temperature) and intrinsic (structure and type of polyphenols and proteins) parameters (Czubinski & Dwiecki, 2017). These factors determine the protein–polyphenol conjugates formed by noncovalent or covalent interactions. Interaction of these components generally affects the functional attributes of food products and eating quality. The interaction between proteins and polyphenols plays an important role in quality improvement of certain food products. For example, protein–epigallocatechin-gallate (EGCG) conjugates have been reported to exhibit better antioxidant activity than unmodified proteins (Gu et al., 2017). Changes in hydrophilic/

hydrophobic balance of the protein might affect the solubility along with other important functional properties including emulsifying, foaming, and gelation properties of the protein–polyphenol conjugates (Rawel, Czajka, Rohn, & Kroll, 2002).

Thermal stability and mechanical properties of gelatine gel could be enhanced via the interaction between proteins and polyphenols (Maqsood, Benjakul, & Shahidi, 2013). An irreversible interaction of quinone with the sulfhydryl and amino groups of proteins and further condensation reactions of quinones will result in the formation of high molecular weight brown pigments. Reaction of quinone with amino group is also known to affect the digestibility and bioavailability of amino acids such as lysine and cysteine (Damodaran, 2008).

Larger phenolic compounds such as the arubigin and the aflavin from black tea showed higher preference for reaction toward milk proteins than flavanol (catechin) monomer because of higher binding sites available for interaction in case of large phenolic compounds (Dubeau, Samson, & Tajmir-Riahi, 2010). Most polyphenols have a distinctive astringency and bitterness that result from their interactions, particularly of procyanidins with glycoproteins of saliva (Dai & Mumper, 2010).

Addition of antioxidant extracts of rosemary in food products can lead to unacceptable flavor and aroma due to the presence of residual volatile compounds such as camphor, verbenone, and borneol (Carrillo & Tena, 2006). Arts et al. (2002) reported the outcome of interaction between flavonoids and proteins on the total antioxidant capacity. It was observed that addition of catechin to β-casein increased the antioxidant capacity of the β-casein solution.

Addition of silver nanoparticles (AgNPs) + guava leaves extract (GLE) solution to corn starch (CS) film caused structural changes between CS matrix through interactions among CS chains and components of the AgNPs + GLE solution (Fortunati et al., 2014).

The application of essential oils (EOs) in food may be limited due to changes in organoleptic and textural quality of food or interactions of EOs with food components (Devlieghere, Vermeulen, & Debevere, 2004). Accordingly, a challenge for practical application of EOs is to develop optimized low dose combinations to maintain product safety and shelf-life, thereby minimizing the undesirable flavor and sensory changes associated with the addition of high concentrations of EOs.

13.3.4 Toxicity

Although plant extracts are used in food applications, toxicological information such as acceptable dietary intake (ADI) and no-observed-adverse-effect level (NOAEL) are unavailable. Owing to problems in standardization of extracts and owing to batch-wise compositional variability, it becomes difficult to assign ADI or NOAEL. The marker compounds in extracts are affected by the variety of plant, geographical origin, plant part used, age, growth conditions, methods of extraction or drying, preparation, packaging, and storage. If the botanical ingredient existed in the market before October 1994, it is then exempted from the food additives category, and the generally recognized as safe (GRAS) status is not mandatory, according to the Dietary Supplement Health and Education Act (DSHEA – Dietary Supplement Health & Education Act, 1994). Some botanicals may not have a history of use as food ingredients but may be derived from sources that have been used in herbal medicinal products in various parts of the world. Examples include *Ginkgo biloba*, Ginseng extract, *Hypericum perforatum* (St. John's Wort). Further, materials with no history of human use such as, phytostanols derived as a by-product from wood, shikimic acid isolated from water-soluble extract of pine needles, may be considered for use in foods, if a checklist of tests to establish safety of phytochemicals added to foods is available (Negi, 2012).

The plant materials for use in food must be consistent with respect to quality and quantity of the active ingredient, and the method of preparation must meet good manufacturing practices. Risk assessment of natural products may require adequate specification of identity and composition as it may be the whole plant, extracts thereof, or purified components. Variability among plant sources, and the process used to obtain the constituents will be a limiting factor in adopting a generic approach to their risk assessment. The nature of the compound, prior knowledge of human consumption, likely exposure, and nutritional impact will determine the approach for toxicological testing of such compounds. Generally, for herbs or complex extracts, it is not possible to make a risk assessment based on a single active component, as more than one component may be of toxicological significance, and the food matrix may affect their bioavailability. A decision tree has been suggested as an aid to the safety evaluation process for plant material intended for food use (Walker, 2004), and general framework for safety assessment of botanicals has been described (Van den Berg, Serra-Majem, Coppens, & Rietjens, 2011).

An antioxidant-rich extract of *Phyllostachys nigra* (Lodd.) Munro leaves containing a high level of polyphenols has been reported to be nontoxic. Acute oral toxicity tests showed that the maximum tolerated dose was greater than 10 g/kg body weight in both rats and mice, without mutagenic effects. A sub-chronic administration for up to 90 days resulted in NOAEL at a dose of 4.30 g/kg per day (Lu, Wu, Tie, Zhang, & Zhang, 2005). When pregnant rats were treated with this extract at NOAEL dose, they did not show significant changes in fertility and gestation index, and there were no effects on embryo-fetal number, viability, sex ratio, and development observed (Lu, Wu, Shi, Dong, & Zhang, 2006).

Triterpenoid-rich extract from stem of *P. nigra* var. *henonis* (Mitford) Rendle showed no toxic effect. The oral maximum tolerated dose was over 10 g/kg body weight in both rats and mice. No mutagenicity was found by Ames, mouse bone marrow cell micronucleus, or mouse sperm abnormality tests. No abnormal symptoms, clinical signs or deaths were observed in rats during a 30-day sub-chronic feeding study using doses up to 830 mg/kg body weight per day. No abnormalities in organ development and hematological parameters were associated with feeding of this product (Zhang, Wu, Ren, Fu, & Zhang, 2004).

The *in silico* toxicophorical analyses were performed to screen the potential hazards of major compounds found in green coffee fruit extracts by Faria et al. (2020). Prediction results did not reveal any toxicological potential for most parameters assessed, with no detected risk of Ames toxicity, carcinogenicity, hERG inhibition, binding to the estrogen receptor, and skin sensitization. In contrast, only a hepatotoxicity risk was predicted for caffeine. Although no toxicity was predicted in the Ames test, which is a short-term bacterial reverse mutation assay, it is known that mutagenic compounds can be formed from trigonelline when green coffee is roasted (Wu, Skog, & Jägerstad, 1997). The compounds were also predicted as noninhibitors of the hERG channel, whose inhibition may lead to ventricular arrhythmia (Priest, Bell, & Garcia, 2008). A nondetected risk was predicted for skin sensitization, a potential adverse effect for dermally applied products (Pires, Blundell, & Ascher, 2015). No binding of compounds to the estrogen receptor was predicted, which may cause disruption of the endocrine system and reproductive toxicity (Shanle & Xu, 2011).

Plants producing pyrrolizidine alkaloids must be mentioned for their harmful effects on human health with hepatotoxic and carcinogenic effects. The risk of accidental contamination of other plants used for animal feed and human nutrition is concrete, as documented by several studies (Li, Xia, Ruan, Fu & Lin, 2011).

13.3.5 Regulations

As procurement of raw materials is the initial step and plays a crucial role in defining the quality of the final product, biological (bacteria, viruses, molds, and related toxins) and chemical (pesticides and heavy metals) contaminants must be stringently controlled. To reduce the risks for consumers, farmers should follow the rules of good agricultural practice for the use of pesticides or fertilizers or comply with the regulations for organic agriculture, depending on the agronomic strategy used (WHO – World Health Organization, 2004). Other factors related to raw materials and potentially contributing to adverse effects are the misidentification of botanicals used in PFS. The main problem is the use of common names instead of the binomial Latin names, as suggested by the Good Production Practices (Tankeu, Vermaak, Chen, Sandasi, & Viljoen, 2016).

Hundreds of plant derivatives are ingredients commonly used in food industry, and they are regulated by the food law as (1) functional food, (2) novel food, (3) traditional food from third countries, and (4) food/dietary supplements. Although there is no international agreement, according to the consensus document on "Scientific Concepts of Functional Foods in Europe" of the European Commission Concerted Action on Functional Food Science in Europe (FUFOSE), functional food is usually considered a product to which one or more ingredients have been added (or more rarely subtracted) with a positive consequence on the functionality of human organs or systems (EFSA – European Food Safety Authority & EFSA Scientific Committee, 2009). It is, therefore, a food that has not only the function of providing calories and nutrients but intends to carry out a favorable action on the consumer's health. This effect must be reached with the quantity of food normally consumed, it must be in "traditional" form (and not in pharmaceutical form) and must guarantee the safety of the subjects taking the product.

Colombo, Restani, Biella, and Di Lorenzo (2020) reviewed that there are numerous food supplements obtained from plants, and most of them are derived from the tradition of use, that is the preparation of infusions or decoctions. Plants have been used by the industries to prepare extracts, to enrich the products with active molecules and enhance the expected positive properties. Supplements may contain a single plant ingredient or their mixture. When greater number of botanicals are present in the finished product, complex problems on correct usage by the consumer and quality control issues arise.

Another critical aspect derives from the fact that there is no harmonization at the international level on the lists of plants allowed in food supplements. Many countries have published positive and/or negative lists of botanical ingredients, which are allowed or prohibited in food/dietary supplements. Unfortunately, there are few correlations between them. The inconsistent situation of the products with botanical ingredients leads to several consequences, including the difficulty in discriminating "healthy" or "therapeutic" information for the same plant used in different product classes. Researchers know that the dose makes the difference, but discriminating the dose with physiological effects from the one that is suitable for clinical applications is a complex objective even for plants of more ancient tradition. These difficulties are reflected in very small number of claims approved by European Food Safety Authority (EFSA) in the field of botanicals. To obtain authorization to associate a nutrition/health claim with a botanical in European Union (EU), the manufacturer must submit a dossier to EFSA, which evaluates the scientific evidence of the studies provided and publishes the relative opinion. The guidelines provided by EFSA – European Food Safety Authority, and EFSA Scientific Committee (2020) describes in detail the studies required for the approval of nutritional/physiological claims.

In the guidelines published by EFSA,

1. "For dietary supplements, food industries cannot claim any therapeutic effect, but only physiological ones"—As a consequence, apart from few exceptions, it is difficult to prove a healthy activity that reduces disease risk factors in the long term.
2. "To obtain statistical significance, it is necessary to recruit a very large "healthy" population that is willing to take a certain product for very long periods"—This is economically unsustainable, and the results could still be affected by the dietary habits of the subjects considered.

It seems unreasonable that the tradition of use has been accepted for traditional medicines and not for food supplements (Colombo et al., 2020).

13.3.6 Economic and ecological costs

Economic analyses performed by McNulty et al. (2020) indicates that the unit production cost of antimicrobial proteins (AMP) in plants at commercial scale is \$3.00–6.88/g. The base case manufacturing facility scenario produces 500 kg of AMP per year at 92% purity including a 42% loss in extraction, downstream processing, and formulation. The base case manufacturing facility requires \$50.1 million capital expenditure (CAPEX) and \$3.44 million per year operating expenditure (OPEX). Upstream and downstream processes represent 58% and 42% of OPEX, respectively. Of the \$2.01 million/year upstream OPEX, the seeding operation represents the majority (79%) of the cost. Chromatography (38%) and ultrafiltration (UF) operations (35%) represent most of the downstream processing OPEX of \$1.43 million/year. The downstream CAPEX accounts for 62% of the overall CAPEX with the clarification and UF units representing the largest portion (49%) of the downstream capital investment costs. Downstream processing is the main contributor to cost of goods sold (COGS) at low production levels, while upstream processing contributes to COGS at high production levels. At 100 kg/year, downstream processing represents 64% (\$8.51/g) of the COGS, while at 1000 kg/year the contribution is reduced to 35% (\$2.15/g) of the COGS.

Economies of scale shows that unit material price decreases as yearly production increases. This becomes a more important consideration when evaluating COGS over a wide yearly production range. In addition, development and regulatory approval of any product to be added to food is a complex, lengthy, and usually costly process.

The utilization of plant extracts is a green and environmentally friendly approach because most of the phytochemicals are water-soluble metabolites like organic acids, quinones, phenolic compounds, flavonoids, alkaloids, catechins, terpenoids, coenzymes etc., including amino acids, plants derived proteins, polysaccharides, and vitamins. Because of their renewable nature, reliable, versatile, biodegradable, biocompatible, and ease of application, several plant extracts have been used earlier (Costa et al., 2015).

However, aspects such as toxicity and bioaccumulation need to be considered prior to their use. Moreover, the effect of solvents selected for extract preparation on the surrounding environment must be considered, as traditional extraction procedures require the use of highly harmful organic solvents. Supercritical fluids represent a new class of alternative solvents for the preparation of plant extracts which permit selective separation of phytochemicals from the extracts at moderate temperatures and optimum processing time (Mari, Bautista-Baños, & Sivakumar, 2016).

13.4 Conclusion

Plants of various species are sources of nourishment and therapeutic formulations for human populations since early times. Evidence indicates that extracts of edible and nonedible parts of plants, herbs, and spices such as leaves, stem, roots, flowers, fruits, and seeds have been in vogue. Aqueous extracts both cold and hot, as well as alcohol based are known, as are lipid based or ash based. A large number have been and continue to be used in traditional systems of medicine. While some are recorded, scientific validation in the current modern paradigm is relatively low. In recent times, the role of bioactive components from such sources, including micronutrients, phytochemicals, botanicals, and prebiotics have become an area of immense interest to health professionals and researchers, contributing to cumulative evidence of their role in health and disease, driving their application in foods and nutraceutical formulations/supplements. The opportunities are multifarious: (1) identification of plant varieties with high levels of the bioactives, (2) development of clean and sustainable extraction methodologies, (3) blending and formulation for optimal beneficial activities, stability, (4) optimization to enhance food quality and safety, (5) function as replacement of synthetic food additives, and (6) add value to existing foods or novel ones.

Leveraging these opportunities will demand appropriate means to address the several challenges. There is an urgent need to develop and harmonize methodologies for the evaluation of these components for their physiological and systemic benefits, while giving due credit to specific scientific issues. These include the level of bioactive component/nutrient; the matrix/food used for the formulation; selection of a representative sample of the study population; their exposure to the food/component; double blinding of both the subjects and the investigators. Continued and concerted efforts by all stake holders are the key to moving forward and deriving the benefits that can be transmitted to consumers.

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