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Review

# The Current Principles Define the Isolation of Health-Promoting Substances from Secondary Herbal Materials

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**Abstract:** Agricultural waste is rich in bioactive molecules. In evaluating the viability of circular models for the development of health-promotional substances and final products, it is important to highlight that the processing industry of fruits and other valuable herbal materials generates a considerable number of by-products and waste containing health-promoting components. These by-products can be utilized purposefully used in pharmaceuticals and related areas for the development of health promotional products. The linear utilization of agricultural waste results in the loss of a range of valuable bioactive compounds, including polyphenols (anthocyanins, flavonoids, phenolic acids, and related compounds), antioxidants from other groups, as well as phytosterols, tocopherols and fatty acids. As an illustrative example, the waste materials of species belonging to the *Vaccinium* genus represent a notable secondary resource that can be purposefully applied to the development of health-promoting substances. The fruits of these wasted herbal materials have been found to contain reliable polyphenols, which play a pivotal role in the prevention of various chronic conditions, including precancerous conditions, inflammatory diseases and other ailments. In addition, the fruits of blackberries, elderberries, and purple corn which are similarly rich in anthocyanins also provide a promising avenue for further developments. Phenolic compounds suitable for recycling are also found in sugarcane harvesting by-products. Tomato waste contains a significant amount of the valuable carotenoid lycopene. The additional value of the above-mentioned fruit processing by-products may attribute to specified physiological functions, which, if used properly, can contribute to the prevention of certain diseases, and improving of quality of life. This review assessed the scope and gaps in the existing principles on the isolation of health-promoting substances from herbal secondary materials.

**Keywords:** refinery; sustainability; fruit cake; seeds; phenolics; anthocyanins; phytopharmaceuticals

## 1. Introduction

The development of health promoting materials is a complex and resource-intensive process, both in terms of scientific experience and economic investment. The integration of various related processes is a crucial aspect of such activities. It is noteworthy that efforts to integrate sustainability aspects universally remain limited in the sphere of the pharmaceutical sector [1].

A variety of solutions may be selected to enhance the sustainability, among which the application of the circular bioeconomy models represents a particularly crucial approach. Over the past decade, there has been a notable increase in the number of research studies and challenges directed at the development of sustainable and/or greener production processes. These processes are designed to achieve two key objectives: firstly, to facilitate the growth of the bioeconomy, and secondly to significantly reduce the negative impacts on the environment and society [2].

At this time, one of the most promising areas for the involvement of health promotional substances in circular bioeconomic models is the isolation and subsequent research of by-products derived from waste originating from herbal sources. It is crucial that bio-refinement of such waste can yield not only a versatile array of biofuels, but also a spectrum of ingredients and products with superior added-value health benefits [3]. For example, the fruit cake and seeds that are remaining after fruit processing are still being underestimated as a source of health-promoting compounds. Although such residual seeds are rich in phytochemical compounds which have a variety of health-promoting properties conventional utilization of fruit seeds often is not rational [4]. The use of residual seeds like other valuable herbal waste in the pharmaceutical and functional food industry can not only help to solve waste problems, but also generate additional revenue for fruit processing facilities. However, further research is required to achieve this goal, as numerous of the nutritional components of fruit seeds remain to be identified [5]. One of the reasons for the continued debate surrounding the concept of recycling is the absence of a comprehensive and rigorous examination of secondary materials. Without such an examination, the urgency of the need for solutions and further tasks to achieve an appropriate result cannot be accurately projected. This is since only through a comprehensive definition and understanding of the scientific and technical progress surrounding the isolation of health-promoting substances from secondary herbal materials can the urgency of the need for solutions be accurately gauged. The aim of review was therefore to identify the scope of scientific knowledge in this area.

### *2.1. A Circular Economy Model for the Development of Health Promotional Products*

The proposed bioeconomy models support the hypothesis of an effective closed-loop approach in which waste from human activities recycled through the steps of circular processes [6]. In the case of circular models, new ways of capturing of value can be developed (foremost through the reuse of materials) [7–9]. In light of these considerations, the circular bioeconomy has been defined as the production of renewable biological resources and the conversion of such resources into value-added goods [10]. Such widely accepted principles are purposeful and supported. For example, the framework of the European Commission sets out targeted strategies to reduce misuse, also reuse, recycle and reclaim [9,11,12].

The integration of the circular principles in the inert sectors of the bioeconomy (such as the development of health-promoting products) necessitates substantial modifications to the prevailing system, encompassing both production and consumption activities [2,9]. Major reforms must aim reducing the barriers and bottlenecks. It is imperative that contemporary economic solutions are appropriately expanded to facilitate the conservation of natural resources and to manage the existing inequalities in the availability and consumption of more sustainable health promotion measures. It would be beneficial to integrate the principles of the bioeconomy into the design and development of health promotional products, with the aim of providing sustainable goods and services that utilize renewable biological resources and processes. [13].

In their 2019 study, Vermundt and colleagues identified potential challenges that may impede the implementation of circular economic models within specific sectors of the economy [9]. It can be reasonably argued that some of the aforementioned factors are undoubtedly relevant in the field of production of health promotional products. The researchers identified several key challenges, including administrative burdens, infrastructure and management shortcomings, a lack of competence and knowledge, and the limited volumes of raw materials currently available. Additionally, the lack of awareness, resistance from market participants in the linear economy, regulatory policies, and limited support for the development and registration of quality products should be noted. Infrastructure and equipment design barriers are less likely to be significant issues in the sector of products closely related to agricultural sources, such as herbal origin by-products. In the field of herbal-based health products, remain a few unfavorable factors, which require further action to be taken to be effective management. In a study published in 2021, Donner and colleagues identified five categories of such factors in the agricultural sector that are related to the production of secondary materials suitable for use in the manufacture of health-promoting products. [2]. Firstly,

scientists concentrated on the technical and logistical aspects of the process, given that innovative technologies frequently required the implementation of novel, sufficiently complex methodologies to obtain valuable biomolecules or high-quality materials. Concurrently, effective and adaptable logistics and substantial storage capacity are highlighted, given the heterogeneous and variable quality of agricultural resources. Regarding the second category, it is evident that further investment in research and development is required. The prices of new biological products are lacking in competitiveness and thus require regulation. The third category of factors encompasses organizational and spatial factors, whereby the optimal conditions for success entail a suitable geographical proximity of entities. The fourth category of factors is institutional and legal. Unfortunately, in the case of health promotional products, these factors have the potential to be the most disappointing, as they are not sufficiently discussed or highlighted. The current and regulatory inequities in the management of agricultural waste, coupled with the difficulty in predicting changes in individual regions, can give rise to significant risks. From the perspective of the health promotion market, even targeted modifications aimed at enhancing the sustainability of traditional herbal pharmaceutical products can prove to be significantly challenging, as they must navigate a multitude of obstacles before reaching the market. The development of this market is subject to several barriers, including the validity of regulatory decisions and restrictions on the promotion and wider inclusion of medicinal herbals in basic healthcare [14]. The promotion of a green economy requires not only corrections to the current situation, but also a purposefully formed regulatory environment. A further (fifth) category of factors is related to the attitude of society towards “green” products and processes. It was noted that companies implemented circular models faced low acceptance and trust in circular products by customers. This problem has often been addressed by actively raising awareness and strengthening of legitimacy [9]. It has always been necessary to provide evidence that products are safe for consumers and the environment. In the context of health products, the potential for adverse consequences may emerge from the perspective of admissibility, encompassing both prejudices and policies within the domain of health promotion.

## *2.2. The Concept of Herbal Waste Recycling and Green Chemistry in Circular Models*

The process of isolating of bioactive substances from herbal waste that remains after processing of food products may play a vital role in the circular bioeconomy of the future [15]. The European Union’s action plan for the circular economy identifies food waste as a priority area for intervention [2,16]. In addition, the researchers have indicated that 1.3 billion tons of global food waste are landfilled on an annual basis. [10,17]. It was also reported that seven hundred million tons of crop are wasted in Europe every year [2,18]. The fruit processing industry generates large quantities of by-products, including pomace, peels, and seeds [19]. Besides, it is estimated that more than 30% of food is wasted worldwide [20]. Such losses could cost the global economy more than \$900 billion [10]. A substantial proportion of the waste materials originate from herbal sources. Selected herbal materials, such as blueberry processing waste, are already undergoing processing and conversion into a value-added final product [10].

It is evident that the economic viability of the bio-recycling process for such residual materials is contingent upon a few factors, including the initial installation costs, the quality of the waste to be recycled, the quantity of the waste, the efficiency of the waste supply chain, the market price of the products created, and the level of support provided by the government and other stakeholders. [3,21]. The scale and needs of technologies based on resource recovery must also be assessed in the light of the specificities of the regions [22].

Additionally, in the context of pharmaceutical development and related fields, it is crucial to adopt and apply the principles of green chemistry, alongside the secondary utilization of raw materials. Although the concept of green chemistry is a relatively novel field of study, it offers a promising avenue for achieving sustainability at the molecular level [1,23]. By avoiding the use of toxic solvents, reducing the number of production stages, and creating safer processes, it is possible to develop more biologically sustainable pharmaceutical products. Innovative eco-based procedures can be expanded to reduce the costs of time, solvents, and energy [24]. The application of green

chemistry principles to the development of pharmaceutical products offers an attractive value proposition in terms of development and production. Moreover, the principles of reducing dependence on rare and costly primary raw materials may also serve to reduce the environmental footprint and eliminate inefficiencies in activities as relevant to current circular models [9,25,26].

2.3. *Types of Secondary Herbal Raw Materials*

The fruit processing industry produces various by-products and waste which disposal is a global challenge [3]. For example, one of the by-products suitable for processing are fruit seeds (Table 1).

**Table 1.** Main secondary herbal materials can be used for the health promotional products.

|                                                                  |
|------------------------------------------------------------------|
| Food residues                                                    |
| Fruit pomace and cakes                                           |
| Parts of the fruit (seeds and other)                             |
| Leaves and parts of the plant remaining after collecting of crop |
| Residues of extracts                                             |

With the proper management of secondary herbal materials, the substantial number of fruits and seeds that currently are removed from the home and agri-food sector could be used for the development of pharmaceutical products and cosmeceuticals [13,19]. Currently, fruit seeds usually are poorly exploited in the food industry and are underestimated and often discarded. The composition of these parts of the plants incorporates a variety of phytochemicals that can be utilized in the development of health-promoting products. It is noteworthy that, in addition to seeds, the entire fruitcake is still a subject of scientific inquiry and is not yet widely employed in the creation of health-promoting products [27]. To illustrate, Campalani and colleagues (2020) evaluated the waste generated by one of Italy’s foremost producers of canned fruit [28]. In addition to the production of the final products, the company also generates approximately 80 tons of organic fruit waste (including seeds, pomace, and other byproducts) from blackberries, raspberries, black currants, wild strawberries, pomegranates, and blueberries annually. The remaining waste is primarily composted [28]. Nevertheless, the isolation of bioactive compounds from secondary materials is feasible when appropriate methods are employed. The extraction is a common method for the isolation of such phytochemicals [29]. The waste produced by the processing of citrus fruit consists of the peel, pulp, cake, and seeds that remain after the initial processing. A range of extractable phytochemicals have been identified in this waste, including pectin, essential oil, polyphenolics and flavonoids, carotenoids, oligosaccharides, organic acids, and vitamins [30,31]. It has been reported that approximately 10 million hectares of land are dedicated to citrus production, with the global citrus harvest reaching 98.7 million tons of fresh fruit [31,32]. The phytochemicals derived from citrus waste can be utilized as ingredients in nutraceuticals or phytopreparations, as well as prebiotics or as a source of pectin and fiber. Additionally, citrus phytochemicals can be applied as emulsifiers, encapsulating excipients, components of nanoparticles, and ingredients in natural packaging materials [31,33,34]. Pectin and zein from citrus peel were used to create nanoparticles enriched with the resveratrol. Besides, pectin oligosaccharides, obtained by the partial hydrolysis of pectin, also demonstrate prebiotic properties [31,35,36]. Therefore, the peel of various citrus fruits can be reasonably reused, but most appropriately, in small-scale bio refinement plants for the extraction of pectin, essential oils and other phytochemicals [3].

2.4. *The Presence of Beneficial Antioxidants and Phenolics in Secondary Materials*

Irrational exploitation of processing by-products results in the loss of valuable bioactive compounds. Flavonoids, anthocyanins, other polyphenols and antioxidants as well as tocopherols, important fatty acids, carotenoids and phytosterols are currently the most studied. For example, fruit processing waste from *Vaccinium* species is one of the important renewable resources that can be widely applied to the development of health promotional products. The fruits of *Vaccinium* species contain polyphenols, which play a significant role in the prevention of various chronic diseases,

including precancerous conditions, inflammatory and other diseases [3,37]. Pomaces of bilberries and blueberries are rich in anthocyanins which bioactivity have already been proven by numerous studies. Therefore, such waste may be primary choice for the development of health promotional products. The anti-inflammatory effect is characteristic for anthocyanins, but the literature also confirms wound healing stimulating, antidiabetic, antioxidant, eye retinal protection and intestinal health management, antibacterial and other effects [38–43]. The color properties of anthocyanins (as well as other coloring phytochemicals) can also be important for pharmaceutical purposes. Anthocyanins can be successfully used to color products as they are a natural alternative to synthetic regulated Red 40 dye [44,45].

Hydroxycinnamic acid esters, especially chlorogenic acid, are also found in sufficient quantities in plant waste of *Vaccinium* species [3]. Since about 20-30% of the biomass of the fruit is transformed into pomace, rich in phenols and other active substances, secondary raw materials from species of this genus must be considered as an exemplary tool for phytochemical compounds suitable for industrial use [3,22,46,47].

Significant concentrations of anthocyanins have also been observed in other dark-colored fruits and vegetables that can be processed in considerable amounts, such as blackberries, elderberries, purple sweet potatoes, and black carrots [45,48–50]. Blackberry fruits are commonly processed into concentrates, jams, and juices [51,52]. About 20% of the fruit mass remain as blackberry pulp [52].

Violet colored maize (*Zea mays* L.) is also a viable alternative for the extraction of anthocyanins due to the high concentration of these phytochemicals (4-10 g/kg) and the low costs of storage and processing. It was highlighted that most of the anthocyanin of purple maize is concentrated in parts which can be easily separated, while the rest of the fruit can be used for food and bioenergy production [45].

High-quality biodegradable remnants remain in the wine industry. The waste of grapes is rich in phenols including flavonoids and anthocyanins with high antioxidant potential [53]. Modified bio-processing methods achieve 71.9 g of grape seed oil and 322.8 g of polyphenols during the processing of 1.0 kg of dry grape marc [3,53].

Apples are widely consumed worldwide. 20-30 % of the total weight of apples consist of solid ingredients such as seeds, cake, and peel [13,54]. Such waste contains bioactive phenolic compounds such as phloridzin, chlorogenic acid and quercetin glycosides, phloretins, epicatechins and procyanidin B2 which are promising compounds for the development of health promotional products, as they have antioxidative and other important properties [54–57].

Valuable phenolic compounds, and with-it flavonoids, also remains in the pulp of sugar cane (*Saccharum officinarum*). Sugarcane flavonoids contribute to the antioxidant and antiproliferative properties [58]. Tricin, one of the sugarcane flavonoids, has been shown to have chemo preventive properties against gastrointestinal carcinogenesis in mice [59]. The remaining materials such as tops, straw, filter cake, molasses and bagasse can be purposefully used not only for the isolation of phenolic compounds, but also for the extraction of various health-friendly lipids (as octacosanol, phytosterols, long-chain aldehydes and triterpenoids) [60].

Common waste products of the canning industry are peels and seeds of tomatoes. Tomato peels contain an important carotenoid lycopene, which is widely used in the cosmetic and pharmaceutical industries [61–63]. Currently, lycopene is produced synthetically or extracted from tomato fruits grown for this purpose. The use of waste products such as peels and seeds for extraction of valuable carotenoids may change such production system from the first to the third generation [64]. It has also been demonstrated that the utilization of cake, a common by-product of the processing industry, can facilitate the production of a range of valuable compounds in the development of functional health products [3,65,66].

## 2.5. Alternative Herbal Secondary Materials for the Development of Health-Friendly Products

It is important to note that, in addition to the cultivation and harvesting of the plants, a variety of other byproducts remain, which can be utilized to create functional ingredients (Table 1). It is estimated that farmers around the world harvest more than one billion tons of different fruits each

year, with millions of tons of different types of waste generated during harvesting and processing, including crushed fruit [3,67]. It was published that most of the waste generated during the production of citrus juice is comprised of peels, which account for between 50% and 55% of the total weight of the fruit, and seeds, which represent between 20% and 40% of the weight of the fruit [31]. In illustration, the cultivation of species of *Vaccinium* results in the production of a considerable quantity of post-harvest biomass, predominantly comprising leaves and twigs that remain following the harvesting process. It is important to note that the phytochemical composition of both food-grade herbs and the leaves of medicinal herbs, as well as other vegetative organs, may be similar or may be characterized by other valuable features. It can therefore be proposed that the utilization of the residual components of the herbal following the harvesting process represents a potential foundation for the establishment of a novel co-destructive processive branch. At present, the fallen leaves of blueberries are typically incinerated or allowed to decompose naturally. However, blueberry leaves also contain phenolic antioxidants. For instance, Debnath-Canning and colleagues (2020) investigated these compounds and discovered that some of the compounds present in the leaves may have anti-inflammatory effects on the nervous system [3,68]. A variety of phenolic compounds were also identified in the leaves of the apple tree, including quercetin glycosides that can be utilized in the production of products designed to promote health and improve wellbeing [69]. Furthermore, the processing of apples generates approximately 20 million tons of non-conventional waste annually, which may encompass not only leaves but also branches and spoiled apples [54].

It is noteworthy that apple pomace comprises soluble and insoluble fiber, including pectin, indigestible oligosaccharides, cellulose, hemicellulose, and lignin [54,70–72]. It has been stated that apple waste may contain up to 51% dietary fiber. Insoluble fiber constitutes 37% of the total, while soluble fiber accounts for 14%. [54,73,74]. It can therefore be concluded that different fiber fractions can be used both together and separately to develop targeted probiotic or eubiotic functionalized formulations.

In addition, cashew apples are recognized as a by-product of the agricultural process, which remains due to the processing of cashew nuts [75]. It is recognized that cashew apples with a bitter and astringent taste are not yet a very attractive commercial proposition. However, in the production of products for health promotion, flavor characteristics would not be the most important factor. The raw material with such characteristics can still be successfully used for the purification of individual bioactive compounds and to produce extracts, provided that the basic aspects of safety of consumption have been properly assessed.

Another promising precursor for secondary use is waste from the processing of plum fruits. The potential for utilization in the production of health-promoting ingredients is supported by the isolation of oil and polyphenols from seeds and pomace [76,77]. The seed shells constitute approximately 86% of the seed weight and, in addition to the seed kernels, can be employed for a variety of purposes, including medicinal applications [78,79].

It would be advisable to devote greater attention to fruit seeds that have not previously been the subject of study or evaluation, and which are consequently frequently discarded. As the example of this are the seeds of dates (*Phoenix dactylifera* L.), which are often discarded as waste. In fact, date seeds constitute as much as 11.32% of the total weight of dates [80].

## 2.6. Bioactivity and Application of extracted Health-Friendly Compounds

The health benefits of fruit seed processing products and their components can be attributed to a variety of biological functions that can help correct health status or prevent disease, thereby improving the quality of life. To illustrate, the researchers' findings suggest the targeted use of essential oil of citrus peels as an antimicrobial or preservative in the pharmaceutical sector [81]. It is worthy to note that the chemo preventive effect was observed in the study of the effect of pomegranate (*Punica granatum* L.) seed oil on mice, the effect of apple (*Malus domestica* L.) seed oil on human lung carcinoma and cervical cancer cells, the effect of mango (*Mangifera indica* L.) seed oil on human breast cancer cell lines, and that citrus seed oils have a inhibitory effect on mouse melanoma cells [19,82–84].

It has been demonstrated that anthocyanin-rich extracts possess the capacity to inhibit the growth of pathogenic microorganisms. An extract prepared from North American raw materials has been demonstrated to inhibit the growth of strains of *E. coli*, *S. aureus* and *L. monocytogenes* [85]. It was established that the extract with anthocyanins exhibits high antibacterial activity, which results in damage of the microbial membrane and acts on target enzymes [85,86]. These findings provide a valuable foundation for assessing the diverse applications of secondary raw materials in the context of antibiotic resistance.

*Punica granatum* L. seed oil, which contains a high content of punicic acid, enhanced the function of mouse B cells in vivo [87]. The antidiabetic activity of methanol extracts of grape (*Vitis vinifera* L.) seeds linked to inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase. It was found that the activity of extracts on  $\alpha$ -glucosidase was higher than of  $\alpha$ -amylase. The co-authors of the study, who published the results, posit that grape seeds may serve as an attractive functional ingredient in foods and may improve glycemia when consumed after meals [19,88]. Given that grape seed extracts possess anticholinergic properties in addition to their antidiabetic effects, the researchers hypothesize that grape seeds may be utilized in the context of neurodegenerative disorders [88].

In a study published in 2019, Athaydes and colleagues evaluated the protective effect of the ethyl acetate fraction of the extracts of avocado (*Persea americana* Mill.) seeds against artificially induced gastric ulcer in mice. The researchers proposed that avocado seed extract could be an appropriate natural source for the prevention and treatment of gastric ulcers [89]. In evaluating the feasibility of extracting and consuming lipophilic bioactive compounds, it is crucial to acknowledge the impact of combined n-3 polyunsaturated fatty acids and herbal sterols on the expression of anti-inflammatory markers. A reduction in C-reactive protein (CRP), tumor necrosis factor A (TNF-A), interleukin-6 (IL-6) and leukotriene B4 (LTB4) and an increase in adiponectin (which plays a role in regulating glucose levels and the breakdown of fatty acids) has been demonstrated in hyperlipidemic individuals because of the use of these isolated compounds [90]. It also should be noted that the conducted systematic review and meta-analysis confirmed the cholesterol-lowering properties of functional products containing phytosterols [91]. When assessing the effect of biorefined octacosanol on fat-rich diets in mice fattened with fat-rich diets, lower body fat gains and liver lipid levels and higher insulin sensitivity were noted, associated with an increase in brown tissue activity and an improvement in liver lipid metabolism [92]. In a study conducted by Lee and colleagues, the effects of octacosanol supplementation were examined in taekwondo athletes who had experienced rapid weight loss due to high-intensity training and calorie restriction. The findings of the study indicated an enhancement in the lipid profile, characterized by an elevation in high-density lipoprotein levels and a reduction in low-density lipoprotein and triglyceride concentrations [93]. Orally administered octacosanol (at doses of 100 mg/kg/day) has been shown to inhibit the expression of inflammatory cytokines in the mouse colitis pattern. Such a mechanism of action is associated with the protective effect of the compound on oxidative stressful reactions in intestinal cells [94].

The flavanones naringin and hesperidin, found in citrus peels, have been the subject of research which has demonstrated their phytotherapeutic and nutraceutical benefits. These compounds have been shown to possess antioxidant, anti-inflammatory and carcinogenic properties [31,95]. Polymethoxylated flavones nobiletin and tangeretin from citrus peels were purposefully studied in treatment of cardiovascular diseases, cancer, resistance to oxidation and inflammation [96,97]. After studying the role of polymethoxy-flavonoids obtained from *Citrus sinensis* peel extract in the treatment and management of gastric ulcer in male rat albinos, was found that during taking the peel extract, the pH of the stomach increased significantly, and gastric acid secretion decreased [98]. In addition, the scientists highlighted the antimicrobial and health-promoting effects of citrus peels, as well as their hepatoprotective, immunosuppressive and cardioprotective properties [31,91,99–101]. It has been demonstrated that the inclusion of *Citrus sinensis* peel extract in the diets of rats has a beneficial effect on their gastrointestinal health [98]. The inclusion of aged citrus peels (*chenpi*) into the diet of rats reduced the body weight and suppressed the increase in fat cells and the accumulation of lipids in adipocytes [103]. Therefore, the bioactive components of citrus waste can be used purposefully to protect from infections, allergies, and other chronic diseases [102].

Restrictions on the use of secondary herbal raw materials for health improvement are based both on the isolation of valuable phytochemicals and on the removal of substances hazardous to health [104]. Cite one example, *Prunus armeniaca* L. (apricot), is widely used in the food industry. However, due to the cyanogenic glycoside amygdalin, including of raw seeds of these fruits for human nutrition or health promotion is limited. It is important to remember that amygdalin itself is non-toxic, but the product of its decomposition (hydrogen cyanide) is poisonous. Therefore, due to the possible toxicity of apricot or other fruit amygdalin-containing seed kernels, fermentation, soaking, ultrasonic action, and microwave should be implemented for detoxifying before consumption [104]. Nevertheless, the elimination of identified hazardous components is inadequate without targeted biomedical studies conducted prior to utilization (studies on genotoxicity, hepatotoxicity, nephrotoxicity, neurotoxicity or chronic toxicity to specific user groups). Given the current lack of understanding regarding the side effects of most herbal ingredients, as well as their potential teratogenic effects during pregnancy, it is imperative to consider the potential impact on this high-risk consumer group [105].

### 2.7. The Current State of the Art in the Recycling of Health-Friendly Compounds

A variety of extraction procedures are employed for the recovery of bioactive components from a seed or pomace matrix [13]. The extraction of phytochemical compounds, such as anthocyanins, from secondary herbal materials may not always be economically viable. This is due to a number of factors, including the potentially excessive costs of raw materials, the high energy needs for storage and processing, and the expected low income from the gross product [45]. One of the targeted solutions is the improvement of phytochemical compound isolation yields and processing techniques. Consequently, there is a perpetual pursuit of more efficacious solutions to enhance the yield of extraction or curtail costs.

When evaluating the classical extraction techniques, it is necessary to mention that not all phytochemical compounds can be successfully isolated by choosing simple technological steps. Wastes typically contain various partially extractable or non-extractable polyphenols that are more strongly or less related to the matrix [3]. Complete and irreversible deactivation of proteins is one of the methods to improve the excretion of phenols. According to the results of published study, an improvement in the extraction process of blueberry anthocyanins was proposed, during which ethanol shock is performed before the final procedures by soaking the blueberry fruit in a 70 % ethanol solution for 1 hour [37].

It was announced that, when selecting technologies for the extraction of lipophilic compounds, developers must consider two primary challenges: firstly, the efficacy of the extraction process and secondly, the complete elimination of non-lipids. Given that phospholipids can form bonds with several biopolymers, and that conventional organic solvents are ineffective at disrupting these interactions, it may be possible to enhance lipid extraction by making adjustments as the modifying of pH during the extraction process [60]. The development of effective bio-treatment technologies in the field of bio-recycling could allow for cost-effective use of this waste and sustainably meet the growing demand for functional ingredients [3,106].

The technology of supercritical CO<sub>2</sub> extraction is an effective method for the purposeful extraction of lipophilic substances. The production of the bioactive compound lycopene using this extraction process was evaluated in tomato pomace [61]. This technology makes possible fractionation of lipids containing various terpenes, phytosterols or tocopherol [107]. The bioactive compounds have been demonstrated to possess anticholesterolemic, antioxidant and anti-inflammatory properties [60]. The available literature suggests that the supercritical method of CO<sub>2</sub> extraction is often more effective than the Soxhlet method using hexane as a solvent in terms of the amounts of lipophilic substances that can be extracted [108,109]. At the same time, carbon dioxide is valued as a greener solvent compared to hexane. It was also found that fatty acids extracted from the seeds and peels of raspberries, blueberries, wild strawberries, pomegranates, blackberries and black currants using supercritical extraction technology were purer and richer in essential fatty acids than in hexane extracts [28]. It is announced that the utilization of supercritical gases is a viable method for the release of certain phenolic compounds. A study was conducted to evaluate the bio refinement

processes of waste from the processing of *Rubus glaucus*. At the biorefinery herbal, phenolic compounds were successfully extracted by a supercritical extraction method. The resulting phenolic compounds were subsequently microencapsulated [3,52].

Increasing the recovery of bioactive compounds can also be achieved by other appropriate technologies. A crucial step towards the sustainability of the process can be the dismantling of complex polymers. Carbohydrates, peptides, and lipids obtained during the chemical and physical process can be used as raw materials for other processes aimed at generating commercially beneficial metabolites. During the biorefinery process, profitable products such as organic acids, natural dyes and other valuable compounds successfully resulted [3,110].

One of the targeted methods to be applied is the fermentation of pomace and other by-products. Rai and colleagues (2021) have announced that it is possible to produce several fermented products with this method, which can have a health-friendly effect [3,111]. The significance of fermentation in the targeted biorefinery of raw materials for health products should be considered in the context of the unique metabolic abilities of unicellular organisms, algae, and microorganisms. These entities possess the capacity to metabolize bioorganic substances present in processing waste. For example, the biotechnological significance of microalgae is attributed to their ability to utilize the carbon, nitrogen and phosphorus produced because of human activity for the biosynthesis of organic molecules. (vitamins, carotenoids, phytosterols, polyunsaturated fatty acids, peptides) [112–114]. The secondary metabolites of the microorganisms themselves, formed during the fermentation process, are also a valuable intermediate product. Since these metabolites play a particularly important role in the competition of microorganisms, in antagonism and in the mechanisms of self-defense, therefore they can also be purposefully exploited in pharmaceuticals, cosmetics or other fields [115,116]. It is appropriate to study and adapt these secondary metabolites in the management of human health problems [117,118].

The advancement of targeted biopolymer substances is also a significant area of interest within the field of pharmacy. To give an example, polyhydroxybutyrate, which is produced by microorganisms, is biodegradable and biocompatible. In a study conducted by Naranjo and colleagues (2014), it was demonstrated that polyhydroxybutyrate can be produced using by-products derived from the agricultural industry. Such a biopolymer may be a suitable replacement for polypropylene and polyethylene in pharmaceutical containers [119].

The treatment of waste products generated during the metabolic processes of multicellular organisms represents a further potential avenue for the exploitation of secondary raw materials for pharmaceutical purposes. The use of target organisms (such as fungi, insect larvae, and worms) allows the process of natural conversion to facilitate the conduction of secretions or parts through these organisms. For example, the use of fly larvae results in the formation of a biomatrix that is rich in compounds with promising biological activity [2]. The offal from fly larvae or other decomposers can subsequently be implemented in accordance with the same principles as secondary herbal raw materials, which are rich in compounds that are beneficial for human health.

In light of the aforementioned considerations, it seems prudent to plan for the utilization of herbal extracts in the context of nano processing, with a particular focus on the synthesis of nanoparticles [120]. In order to achieve the aforementioned objectives, a variety of natural sources may be employed, including parts of selected herbals, isolated phytochemicals of herbal origin, fungi, algae, bacteria, marine organisms, and agricultural waste [13,121]. Due to the rich biodiversity of herbals and their possible secondary metabolites, herbals and herbal parts have recently adapted for the synthesis of various nanoparticles [122]. Nanoparticles can be synthesized using various physical methods including sonochemistry, microwave radiation, laser ablation, and other methods [13]. Biological methods have advantages because they are not complex in comparison with conventional chemical synthesis techniques, and are economically and ecologically viable, since the use of harmful chemicals or reagents is avoided [121]. As a rule, such biogenic synthesis is characterized by minimal environmental impact. Molecules in biological extracts were adapted to stabilize nanoparticles and stimulate nanoparticulation processes [123]. In addition, the extracts can reduce the metal precursor, thus stabilizing the nucleus of nanoparticles [120]. Materials of herbal origin have been successfully

used in recent times for the synthesis of greener nanoparticles of cobalt, copper, silver, gold, palladium, platinum, zinc oxide and magnetite [124,125]. Khatami and Pourseyedi (2015) announced the synthesis of silver nanoparticles from an aqueous extract of date palm seeds [126]. The resulting silver nanoparticles distinguished by antibacterial and antifungal effects. Sakthivel et al. (2022) developed and adapted effective zinc oxide nanoparticles from lemon seed extract [127]. These nanoparticles also increased the rate of regrowth of the tail fin of partially amputated zebrafish. Rafique and colleagues (2021) have shown that nanoparticles can be synthesized using *Citrus reticulata* leaf extract [128]. Nisa et al. (2023) synthesized sustainable magnesium oxide nanoparticles using phytochemicals contained in the hydroalcoholic extract of *Tamarindus indica* seeds [129]. Biosynthetic nanoparticles have studied for their cardioprotective effects in rats to reverse cardiotoxicity caused by doxorubicin. Pre-administration of nanoparticles to Wistar Albino rats has significantly reduce the number of biomarkers of heart damage, such as cardiac troponin-I, aspartate aminotransferase, and creatine kinase.

### 3. Conclusions

The development of health promotion products remains minimally integrated with circular models. Furthermore, the loss of high-value health-promoting materials and the increase in waste have a negative impact on the environment. Technological progress in the classification and characterization of secondary raw materials of herbal origin, the selection of phytochemical targets and the development of purification methodologies currently provide the strongest basis for the identification of new research objects and the promotion of more active scientific involvement and the raising of scientific tasks in areas related to the development and production of sustainable health promotion products. In particular, this approach has yielded tangible results, with some waste from fruit processing already being offered as a raw material for the production of value-added products.

Recently, research has been conducted and attempts have been made to introduce methodologies for the use of the most economically viable secondary herbal raw materials for the isolation of health-promoting antioxidants and polyphenols. A substantial proportion of the ongoing research has concentrated on the development of technologies for the isolation of these compounds, in conjunction with the green synthesis of nanoparticles, which represents an emerging field within the general area of nanotechnology. Extracts produced from herbal residues, agricultural or agro-industrial sources containing peptides, flavonoids and other phenols, alkaloids, saponins, steroids, in most cases, can function as stabilizing and nano-forming agents. The ongoing scientific work and its results provide the basis for preparing for changes in the regulatory environment and for planning various economic activities. Nevertheless, the advancement of this collaborative approach to the development of health-promoting substances and final products and the enhancement of sustainability necessitates not only the involvement of the scientific community, but also the implementation of suitable and timely solutions.

### 4. Future Directions

The development of health-promoting products derived from recovered bioactive compounds represents a significant opportunity within the circular bioeconomy. At present, only a limited number of secondary herbal sources, such as blueberry processing waste, are undergoing partial biorefining and being transformed into value-added products. Technological advances in the classification and characterization of secondary raw materials of herbal origin, the selection of phytochemical targets and the development of purification methodologies can facilitate the identification of novel research objects and encourage greater scientific involvement, as well as the formulation of new scientific tasks in the field of phytopharmaceuticals and in the target branches of medicine and veterinary medicine. Nevertheless, the viability of recycling technologies for valuable waste is influenced by several factors, including the costs associated with their implementation, the quality of the recyclable waste, the efficiency of supply chains, the efficacy of regulatory procedures, and the availability of incentives. It is therefore necessary to conduct a scientific assessment of the current situation and prospects, considering the maturity of society in the transition from linear to

circular models in this area. It is imperative that urgent solutions be implemented to facilitate the integration of phytopharmaceutical and related industries into circular processes. Concurrently, a sustainable regulatory framework must be established to ensure the proper management of health promotion materials of new origin. Reducing waste through the efficient reuse of appropriate herbal origin raw material and efficient recycling of bioactive phytochemicals is one of the main tasks of the growing circular models of the modern and future phytomedicines. By making more extensive use of different resources for the isolation of targeted phytochemicals or fractions enriched with them, it is possible to expand the range of potential health promotional final products. Increasing the recovery of bioactive compounds can be achieved by various modern and targeted technologies, but the greatest viability is characterized by green, cost-effective extraction techniques. However, several decisions should only be seen as a primary stage, since questions have not yet been answered, both about the isolation of significant compounds that are found in small quantities or in quantitatively unstable quantities in waste, and about the exploitation of alternative, less usable secondary raw materials. Furthermore, as with other herbal materials, recycling processes may result in the residual presence of contaminant residues (including products of vital activity of mould and bacteria) or improperly identified components, in addition to the active substances. It is therefore imperative that a comprehensive quality control, comprising physico-chemical and biological analysis, be implemented throughout the entire production or processing of secondary herbal raw material. This encompasses the cultivation of herbs, harvesting, drying and storage, processing procedures, preparation of extracts, and the production of the final product. Nevertheless, despite the implementation of an appropriate preparation process, it is still possible for physico-chemical and pharmacological interactions to occur. The detection and investigation of these interactions can only be conducted during the clinical examination (or administration) of the product. The appropriate utilization of non-conventional materials requires a more comprehensive evaluation, although the potential for their incorporation should be considered favorably. It is important to carry out biological research on the activity and safety of compounds, as this will provide a basis for developing various strategies and contribute to the assessment of how value variations will be perceived and developed. In addition to the points, it is crucial to consider the potential viability of implementing such circular models in the future. This should include an emphasis on the co-production of health-promoting bioactive molecules, particularly given the increasing prevalence of supply disruptions and isolation, as seen in the context of escalating long-term conflicts. In order to develop more distant future directions for this concept, it is essential to conduct scientific research to substantiate its utilization in space exploration programs, particularly in relation to the potential deterioration of quality of life on our planet.

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