REVIEW

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Recent Advances in Research on Polyphenols: Effects on Microbiota, Metabolism, and Health

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This paper is dedicated to the memory of our dear colleague Carolina Rojas-Garbanzo who passed away prior to the submission of this manuscript.

Polyphenols have attracted huge interest among researchers of various disciplines because of their numerous biological activities, such as antioxidative, antiinflammatory, antiapoptotic, cancer chemopreventive, anticarcinogenic, and antimicrobial properties, and their promising applications in many fields, mainly in the medical, cosmetics, dietary supplement and food industries. In this review, the latest scientific findings in the research on polyphenols interaction with the microbiome and mitochondria, their metabolism and health beneficial effects, their involvement in cognitive diseases and obesity development, as well as some innovations in their analysis, extraction methods, development of cosmetic formulations and functional food are summarized based on the papers presented at the 13th World Congress on Polyphenol Applications. Future implications of polyphenols in disease prevention and their strategic use as prophylactic measures are specifically addressed. Polyphenols may play a key role in our tomorrow´s food and nutrition to prevent many diseases.

1. Introduction

More than 8000 phenolic compounds, plant secondary metabolites, have been studied so far and classified into stilbenes, phenolic acids, flavonoids, and lignans.[1] A large part of them has been identified in human nutrition; they are indeed the most abundant plant-derived phytochemicals in our diet.[2] Some polyphenols (PP) such as quercetin, are found in most plant sources (fruits and vegetables), while others are less ubiquitous. For example, citrus fruits are rich in flavanones and apples contain high amounts of phloridzin.[3] PP are known for their diverse biological activities, such as antiradical, antibacterial, anticancer, antioxidative, and anti-inflammatory

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properties.[4] According to various reports, raw plant extracts containing a large number of the above-mentioned substances could have the same or even a stronger health-promoting effect than their isolated individual components.[5] Many applications have therefore been suggested to explore the potential of PP use in therapeutics, cosmetics, dietary supplement, and food industries. The present review thoroughly encompasses up-to-date research on polyphenols interaction with the gut microbiota and the mitochondria, on their metabolism and role in cognitive diseases and obesity, as well as their analytical aspects, extraction methods, cosmetic products, and functional food conception (**Figure 1**). It summarizes select contributions to the 13th World Congress on Polyphenols Applications held in Malta in September 2019. The reviewed topics are supplemented with updated findings published following the Malta conference. Roughly one-fourth of the cited papers was published prior to 2015, one-half in the period 2016–2019, and one-fourth in 2020 and 2021.

Positive synergistic effects of polyphenols on human health and their promising potential in protecting against chronic diseases could lead, following the corresponding clinical studies, to a reconsideration of these valuable molecules in future strategic management of disease prevention.

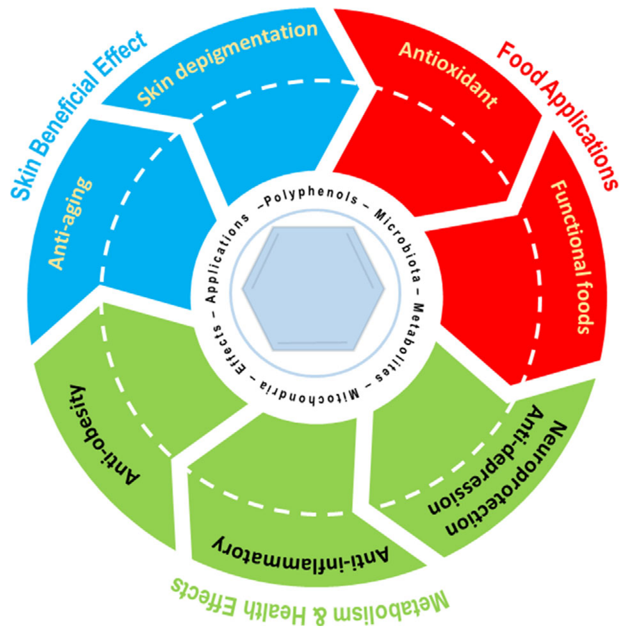

Figure 1. Beneficial effects of polyphenols and their metabolites, and their potential application in cosmetics, food, and health.

2. Microbiota Interactions, Metabolism, and Health Effects of Polyphenols

2.1. Effects of Polyphenols on Mitochondria, Neuroprotection, and Healthy Aging

The increased life expectancy of the population is a global trend with dramatic impacts on public health due to the prevalence of metabolic and neurodegenerative diseases, including type 2 diabetes and Alzheimer's disease (AD). Currently, there are few disease-modifying treatments available for AD.[6,7] Many suggested novel therapeutics, which were at the heart of drug development programs, have so far failed in the clinical trials.[8] Hence, there is a growing interest in preventive strategies, highlighting the importance of diet and physical activity in supporting the healthy aging of the brain and preventing AD.[9,10]

Mitochondrial dysfunction has long been associated with aging and age-related disease development.[11,12] A decrease in mitochondrial function and thus the loss of sufficient energy production is thought to play a key role in age-related decline. Development of methods to prevent mitochondrial dysfunction is therefore an effective strategy to counteract the negative effects associated with aging.[13–16]

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The long-standing quotidian intake of PP was shown to alleviate the age-related cardiac effects such as inflammation and cell apoptosis while preserving the morphology of the heart.[17] Moreover, grape pomace PP were suggested as potential therapeutics since they modulated the transient receptor potential canonical 3 - nuclear factor of activated T cells c3 (TRPC3-NFATc3) signaling and regulated ventricular cardiac fibroblasts and myocardial fibrosis.[18]

2.1.1. Correlation Between Olive Oil Consumption and the Prevention of Neurodegeneration

In recent years, physical activity and dietary patterns rich in polyphenols, such as the "Mediterranean Diet," have extensively been shown to be important in stimulating the brain and mitochondrial capacity and in improving overall health.[19,20] An important component of "Mediterranean Diet" is the high consumption of extra virgin olive oil, which appears to enhance cognitive functions.[21,22] Extra virgin olive oil contains a variety of terpenoids and polyphenols, including secoiridoids, phenolic alcohols, lignans, and flavonoids, which exhibit neuroprotective properties during the aging process.[22] Hydroxytyrosol and oleuropein are two of the most important antioxidants in olives having neuroprotective properties.[24–26] Recently, ligstroside, a secoiridoid occurring in young olives, was shown to be highly protective against mitochondrial dysfunction in SH-SY5Y cells expression human APP695 and aged naval medical research institute (NMRI)-mice as models for early AD and brain aging, respectively.[26] Olive polyphenols from olive leaves and extra-virgin olive oil have therefore been proposed as promising new agents to combat age-related neurodegeneration.[27]

2.1.2. Action Mechanism of Polyphenols in Neuroprotection

Numerous preclinical studies have investigated the effects of raw plant extracts or isolated polyphenols on cells and animal models of AD. Polyphenols such as resveratrol or protocatechuic acid are known for their antioxidant, anti-inflammatory, anti-apoptotic, anticarcinogenic, and mitochondrial modulating properties and have therefore been frequently studied as related to ageing and mitochondrial function.[23,29,30] Recent evidence suggests that PP exert their neuroprotective effect through the induction of survival mechanisms similar to caloric restriction and physical activity, including the stimulation of longevity signals that goes beyond antioxidant properties and include sirtuins and mitochondrial biogenesis.[31–33] Using amyloid precursor protein/presenilin 1 (APP/PS1) mice as a preclinical model of AD, Sun et al. (2021) found that the hops flavonoid, xanthohumol, ameliorates memory impairment, and reduces β-amyloid deposition in the hippocampus of APP/PS1 mice via regulation of the mechanistic target of rapamycin/microtubule-associated protein 1 light chain 3 II (mTOR/LC3II) signaling pathways.[33]

2.1.3. Effects of Polyphenol Metabolites on Mitochondrial Functions and Healthy Aging

Despite the numerous health beneficial effects of polyphenols, many clinical studies were not able to demonstrate a link between positive effects of PP intake and circulating PP levels. This is likely due to the low bioavailability and the extensive metabolism of PP leading to a diverse metabolite spectrum. After ingestion, PP undergo a series of complex chemical reactions through the metabolism of the microbiota and—after absorption—through the classical phase I and phase II metabolism in hepatocytes and enterocytes.[37–39] Moreover, this metabolite spectrum can greatly diverge at an inter-individual level, since the colonization with microorganisms can depend on the individual situation.[37]

Therefore, in order to conduct accurate biomedical investigations, the identification and determination of PP metabolites in tissues and the use of metabolites in in vitro studies are necessary.

Accordingly, the effects of a bacterial phenolic metabolite mixture produced by the fermentation of fruits and vegetables by *Lactobacillus rhamnosus* and *L. casei* were tested in the invertebrate animal model *C. elegans*.[32] In nematodes, the phenolic metabolite mixture and the metabolite protocatechuic acid promoted molecular and cellular aspects of longevity, in particular mitochondrial function, which could be beneficial for optimal health, thus contributing to healthy aging.[32] Protocatechuic acid in particular has antioxidant properties and shows positive effects on mitochondrial function and energy production.[38] Recent evidence indicates that also other phenolic acids that represent PP metabolites such as gallic, vanillic and syringic acids activate longevity pathways in *C. elegans*.[39] Since mitochondrial dysfunction contributes to both aging and non-communicable diseases, it is an important target for PP. However, to precisely estimate the intake of PP in clinical studies, the quantification of biomarkers is required. Furthermore, a comprehensive understanding of the biotransformation of PP and the identification of the different metabolites in the human body is indispensable. Many studies showed that PP are able to modulate mitochondrial metabolism, biogenesis, and redox status.[40] However, transferring the doses used in in vivo studies to human studies is a major challenge. This is especially true for studies in invertebrates. For rats and mice, dose-response relationships are known to some extent from pharmacological studies. Nevertheless, PP and their metabolites have a great potential to influence human health through the diet when the known obstacles such as low concentrations, lack of bioavailability, and extensive metabolism are taken into consideration.

Therefore, strategies to enrich polyphenols and their metabolites in food, to increase bioavailability and to restrict metabolism should be investigated in the future, finally resulting in human studies. Tools, for example, to increase bioavailability are known to improve the stability of PP as well as their solubility, e.g., by addition of piperine, incorporation into micelles, complexation with cyclodextrin, or liposomal and nanotechnology formulations.

2.2. Effects of Polyphenols on Gut Microbiota

Besides the important impact of PP on mitochondria and in neurodegenerative disease prevention, a substantial impact of PP was also demonstrated through their interaction with the gut microbiota.[44,45]

PP interact with the host metabolism, physiology, and health, playing a crucial role in the protection against pathogenic infections, in the stimulation of the immune system, and the regulation of oxidative stress. An imbalance of the bacterial quantity and quality in the gut microbiota was linked to several pathologies. New strategies were developed for the manipulation of the microbiota; these include fecal transplantation, phage therapy, the use of pre/probiotics, and the adoption of an appropriate diet.[43] The importance of studying microbiota lies in the possible relationship between its composition and the brain, through the signal-mediator metabolites that are produced by these bacteria. For example, butyrate, a short chain fatty acid (SCFA) produced by the bacteria during the fermentation of fiber, can fuel and boost mitochondria and improve brain health. Similarly, dietary PP were shown to interact with the human and animal gut microbial communities, *Lactobacilli* and *Bifidobacteria*, enhancing butyrate production to reduce colitis and prevent colitis-associated colorectal cancer, and decreasing in parallel the presence of pathogenic microbes.[44] Recently, it was highlighted that the microbiota releases metabolites such as hydrogen sulfide (H_2S) and nitric acid (HNO_3) as well as SCFAs that can interfere with the mitochondrial respiratory chain and adenosine triphosphate (ATP) production, and can affect gene expression in particular of inflammatory cytokines.[45] The quality of the human microbiota and the dynamics of mitochondria can be re-modulated and manipulated by diet and/or metabolites to restore the equilibrium and homeostasis of the system. The quality of the metabolites depends on whether they are derived from “good” or “bad” gut bacteria (**Figure 2**).

The positive impact of PP was also attributed to anti-inflammatory metabolites produced by the gut microbiota, leading to a reduction in the symptoms of inflammatory bowel diseases. All these advantageous aspects are suggested to be a synergy between the impacts of their metabolites on the increase of

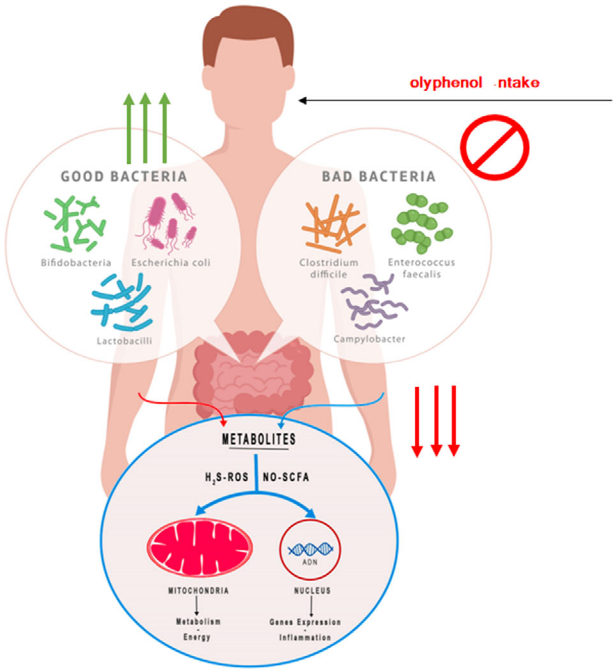

Figure 2. Effects of a polyphenol-rich diet on the host via the metabolites produced by the microbiota. The quality of the metabolites depends on whether they are derived from good or bad gut bacteria.

beneficial microbial diversity while inhibiting the opportunistic pathogenic ones by oxidative stress reduction mechanisms.[49–52]

2.3. Effects of Polyphenols on Obesity

Society needs innovative anti-obesity strategies that cause a significant reduction in food intake and/or an increase in energy expenditure with higher efficacy, safety, and selectivity. The discovery of leptin in 1994 opened a new field within the therapeutic strategies driven to combat obesity. However, the administration of leptin is inefficient in decreasing the body weight of obese mammals who are not leptin-deficient but instead have high levels of circulating leptin associated with loss of responsiveness to this hormone.[50] This hyposensitivity to leptin and its prevention and treatment could represent a major challenge in obesity research for the next decade. In this sense, during the last years, potent leptin sensitizers, such as betulinic acid, celastrol, and withaferin A, were identified.[51] In addition, the wide protective effects exerted by polyphenols on obesity models, targeting several of the multifactorial disorders associated with obesity, allowed us to hypothesize that polyphenols or polyphenol-rich fruits might have the potential to modulate central and peripheral leptin signaling and, thereby, restore leptin sensitivity.

Certainly, different types of polyphenols can ameliorate energy homeostasis in obesity partly through the modulation of leptin signaling. Among others, procyanidins were able to reduce the circulating level of leptin not only by reducing its secretion but also by promoting the activation of signal transducer and activator of transcription 3 (STAT3) in the hypothalamus in cafeteria diet-fed rats by increasing silent information regulator 1 (SIRT1) activity.[52] Another compound that can be highlighted is resveratrol, which reduces hyperleptinemia and activates hepatic STAT3 in a SIRT1-independent manner as well as increases the leptin receptor protein content in palmitate-cultured hepatocytes.[56,57] The principal prenylated flavonoid from hops (*Humulus lupulus*), xanthohumol, was shown to reduce weight gain in leptin signaling-deficient Zucker rats and in high fat-diet fed C57BL/6J mice.[58–60] The authors did observe a PP-related reduction in leptin levels, but the reduction had no effect on food intake. Based on difference in metabolomics and lipidomics profiles between PP-treated and untreated animals, the authors concluded that the anti-obesity effect was due to mild mitochondrial uncoupling and the resulting increase in β-oxidation of fatty acids.

Camellia nitidissima Chi flower extracts rich in PP were shown to have potential anti-obesity and weight reduction impacts on rats. The mechanism was attributed to appetite reduction and interaction with the gut microbiota. PP decreased the quantity of *Firmicutes* and increased that of *Bacteroidetes* and *Verrucomicrobia*.[58]

Different protective effects of grape pomace and grape pomace extract on the alterations related with overweight were commented.[62,63] In the same context, the compounds/metabolites that reach plasma and tissues after an acute dose of extracts administrated to rats were presented for the first time, particularly for metabolites of *trans*-resveratrol and quercetin in plasma.[61]

Long-term treatments with GPE could help in the evaluation of the presence of other types of metabolites in tissues. For example, those produced after digestion processes or microbiota action. These types of studies in animal models or ideally in humans will be important to provide new insights related to the kind and concentration of metabolites present in tissues. In addition, this data will help to understand which metabolites are related with the observed biological effects.

Polyphenols are therefore a very promising class of natural products that can potentially be used to reduce obesity. Hence, it is convenient to emphasize their potential suitability for incorporation in functional foods formulations directed towards weight reduction.[62]

2.4. Effects of Polyphenol on Stress-Induced Psychological Impairment

There is a rising interest in the therapeutic role of PP to modulate neurobehavioral disorders by affecting the gut microbiota and the brain. Natural PP were shown to have anti-stress effects in some in vitro and in vivo models.

A study explored the role of two selected phytochemicals, dihydrocaffeic acid (DHCA) and malvidin-3-*O*-glucoside (Mal-gluc). These compounds were identified through high-throughput screening of bioactive compounds from a polyphenol-rich preparation and were shown to promote resilience against stress-mediated depression-like phenotypes by modulating systemic inflammatory responses and brain synaptic plasticity. Results showed that treatment with DHCA/Mal-gluc also significantly reduced depression-like phenotypes in a mouse model of increased systemic inflammation induced by transplantation of hematopoietic progenitor cells from stress-susceptible mice. This study sheds light on novel molecular crosstalk between peripheral and central pathophysiological cascades as novel therapeutic targets, and the use of polyphenols as a therapeutic agent for treating depression.[65–67]

Oral treatment of rats with selected PP (xanthohumol, quercetin, and phlorotannin) prevented maternal separation-related depression and anxiety behaviors. Xanthohumol administration deeply changed the composition of the microbiota and reversed some altered microbiota-brain pathways associated to rats suffering from maternal separation. Natural PP therefore exhibited anti-anxiety-like impacts on early-life stressed rats by a suggested mechanism implicating the hypothalamo-pituitary-adrenocortical regulation.[66]

Metabolic improvements in C57BL/6J mice orally treated with xanthohumol and its hydrogenated derivatives were shown to be linked to alteration of the gut microbiome and gut microbe-associated bile acid metabolism.[67] The xanthohumol-treated obese mice exhibited better cognitive performance than the control mice in the Morris water maze that test for spatial memory and learning.[68] In a mechanistic follow-up study, the authors attributed the memory-improving effects to xanthohumol-induced lowering of hepatic and hippocampal levels of ceramides, which are known to impair cognitive function.[69]

2.5. Effects of Polyphenols on Inflammation and Allergy

Inflammation is at the root of several biological processes and, in the last years, a complex interplay between inflammatory events and allergic reactions has been acknowledged. Phlorotannins are phloroglucinol-based polyphenols found in brown seaweeds (Ochrophyta, Phaeophyceae) that have stood out as high-value bioactive compounds and potent modulators of several biochemical processes linked to the breakdown of homeostasis in major chronic diseases. Phlorotannin-targeted extracts from the seaweed species *Fucus guiryi* G.I. Zardi, K.R. Nicastro, E.S. Serrão & G.A. Pearson, *Fucus serratus* Linnaeus, *Fucus spiralis* Linnaeus, and *Fucus vesiculosus* Linnaeus were characterized by high performance liquid chromatography equipped with diode array detection-mass spectrometry (HPLC-DAD-ESI/MS)^n and ultra-performance liquid chromatography coupled to electrospray ionization quadrupole-time of flight mass spectrometry (UPLC-ESI-QTOF/MS).[70] Their in vitro anti-inflammatory and anti-allergic potential was then addressed.[73–74] Besides inhibiting the activity of eicosanoid-metabolizing enzyme arachidonate 5-lipoxygenase (5-LOX), the overproduction of the pro-inflammatory mediator nitric oxide (NO) was also efficiently surmounted by the phlorotannin-targeted extracts.[71] They were also able to act upon critical steps of the allergic response, reducing basophils' degranulation and inhibiting hyaluronidase activity.[72] In general, the unique phlorotannin profile, both in qualitative and quantitative terms, was behind the observed bioactivities, evidencing the multitarget capacity and the potential of these marine algal polyphenols as promising therapeutic assets.

Despite the high potentialities already ascribed to phlorotannins, information on phlorotannin bioavailability is still scarce and a major limitation to fully understand their bioactivity and mechanism of action in vivo. Therefore, it has been useful to consider the absorption and metabolism of plant-derived polyphenols. In this case, the anti-inflammatory and antiallergic activities were determined in vitro, using well-documented cell-based and cell-free models of disease, pointing to the potential of these marine polyphenols to act in multiple biological targets. In fact, in a previous report by Corona et al. (2016), gastrointestinal modifications in vitro of seaweed phlorotannins from *Ascophyllum nodosum* (L.) Le Jolis led to the detection of several phlorotannin metabolites that were capable of acting on inflammatory markers, such as IL-8, suggesting it as a possible target for phlorotannin bioactivity.[73]

Overall, phlorotannins arise not only as promising bioactives but also as a still unexplored class of compounds, which represents clearly a valuable research opportunity. Nevertheless, before becoming a reliable therapeutic option, bioavailability issues need to be overcome.

Rubus suavissimus S. Lee polyphenol extracts were also shown to attenuate an egg-induced allergic response in mice through the regulation of IL-4, IL-10, IL-12α and INF-γ, IgA, histamine, and mouse mast cells protease-1 (MMCPT-1). Results suggested the potential design of a polyphenol-enriched functional food implicated in the management of food allergies.[74]

3. Polyphenols and Food

The extraction process is a primary step that achieves PP recovery from different matrices. It plays a major role in the preservation of the PP biological properties for their subsequent applications in food, nutriceuticals and cosmetics. The current trend in PP extraction is leaning towards the valorization of food byproducts using energy-saving innovative "green" technologies to meet the sustainable development concept.[76–80] The extraction and characterization of polyphenols from viticulture (grape canes) and winemaking byproducts (grape pomaces and stems) was recently reported. The phenolic composition of these byproducts from different grape varieties were presented. The Malbec grapes showed the highest potential in terms of antioxidant capacity and composition. In addition, good correlations between individual phenolic compounds and antioxidant capacity of extracts were observed.[81–84]

3.1. Identification of Non-Extractable Polyphenols in Food Matrices

Numerous foods, among them tropical fruits, have gained attention due to their use in traditional medicine, and several marketing strategies were developed to promote their health beneficial effects.[84] This has led to the assessment of studies focused on the identification and quantification of compounds such as polyphenols.[85,86] Recently, fruits of the genus *Psidium*, which are originally from Mesoamerica, were of great interest and different groups of polyphenols were described.[87–90] Specifically, condensed (proanthocyanidins) and hydrolysable tannins (ellagitannins and gallotanins) were reported to be the main polyphenols in pink guava (*P. guajava* L.) and Costa Rican guava (*P. friedrichsthalianum* Nied.), representing more than

70% of the total extractable polyphenols.[89,90] More recently, it was found that non-extractable polyphenols (NEP) reached more than 60% of the total polyphenols present in these two species. NEP are constituted mainly by phenolic acids and polyphenols with high molecular weights, i.e., proanthocyanidins and hydrolysable tannins, presenting interactions with the components of the cell wall (fiber, hemicelluloses, cellulose, lignin, pectin, and proteins).[90] This condition makes these compounds less bioavailable in the small intestine and more available for digestion by the intestinal microbiota in the colon.[91] The resulting gut microbial metabolites are the ones responsible for the potential bioactivities on human health. In order to perform in vitro and in vivo studies, the main common and the most discriminating compounds among fruits must be identified. Thus, (un)targeted statistical assessment was recently used for determining the main metabolomic pathways occurring in plants. This approach was applied to polyphenols previously characterized in pink and Costa Rica guava and allowed the recognition of the gallotannin eucaglobulin as the most discriminating compound. This polyphenol was present only in one of the two species, that is, *P. guajava*, while the bezophenone guavin B was also considered as a discriminating compound but due to differences on concentrations. Regarding polyphenols in common, the ellagitannin geranin was found to be present in both fruits showing similar concentrations; that means, pink guava and Costa Rica guava may be used indistinctively as a source of this polyphenol. With this information, further studies focused on evaluating the effect of processing may be more precisely assessed. Moreover, specific strategies for the development of functional foods, and determination of the bioavailability and bioabsorption of polyphenols as well as their metabolites can be applied.

3.2. Polyphenols Bioavailability

In the case of grape canes and stems extracts, additionally to phenolic and antioxidant characterization, an in vitro study evaluated the stability and potential bioaccessibility of polyphenols under simulated digestive physiological conditions. The most highlighting trend was observed for stilbenes, particularly for ϵ-viniferin (the most abundant polyphenol detected in canes), for which a substantial increase in bioaccessibility was observed (137%).[83] As far as ϵ-viniferin is concerned, no previous studies on its stability are present in literature and the data indicated that ϵ-viniferin is nonsignificantly degraded by digestion in simulated intestinal fluid. The high bioaccessibility observed, specifically in cane extracts, will help to better know the bioactive potential of this by-product. Additional studies to understand the possibility of absorption of highly bioaccessible compounds such as ϵ-viniferin are necessary for promoting new applications.

Additional research should be focused on understanding the effects of the presence of other nutrients, such as proteins, fiber, lipids, carbohydrates, minerals, and others on the modification of bioaccessibility of some compounds. Complementing these types of studies, it could be essential in a following step to conduct an in vivo evaluation of the bioaccessibility of polyphenols in human models with the aim to understand the potential application and doses to be used.

3.3. Dietary Polyphenols and Health: a Machine-Learning Approach for PP Identification

There is overwhelming evidence from epidemiological observations that diets rich in fruits and vegetables have a positive impact on human health. As many fruits and vegetables are rich sources of polyphenols, researchers have developed the hypothesis that dietary polyphenols are responsible for those beneficial health impacts.

To substantiate this hypothesis with scientific evidence, researchers have reported thousands of studies showing antioxidant, anti-inflammatory, anti-hyperlipidemic, anti-bacterial, and cancer-related effects of whole polyphenol-containing foods, food extracts, and individual polyphenols in various, mostly preclinical models of disease. While such studies have generated a wealth of new information, they have largely not been successful in identifying causal relationships between exposure to dietary polyphenols and improving or maintaining health. As it will not be possible or at least impractical to study the health effects of all or even a subset of individual polyphenols present in foods in randomized clinical trials, researchers need novel approaches to link dietary polyphenols to human health. The conventional method to identify bioactive phytochemicals in plant extracts is bioassay-guided fractionation. This approach is time-consuming and labor-intensive. As presented by Stevens, his group of collaborators combined machine learning with experimental characterization of plant extracts with the aim of detecting phytochemicals that predict bioactivity without the need for isolation of those phytochemicals.[92] The authors presented results from a hops (*Humulus lupulus*) extract as an example. Several preclinical and clinical studies showed that a prominent polyphenol from the resin fraction of hops, xanthohumol, is bioavailable following oral administration in rodents and humans.[93–95] Many types of biological activities were attributed to this prenylated flavonoid over the past few decades.[97,98] The authors have demonstrated that oral treatment of animals with xanthohumol in pure form has repeatedly resulted in improvement of biomarkers of metabolic syndrome in rats and mice, such as lowering systemic chronic inflammation.[59–60] It was still unknown whether xanthohumol is the predominant anti-inflammatory compound of hop extracts because pure xanthohumol was tested accompanying minor prenylated polyphenols in preclinical models.[98] To understand which constituents contribute to the anti-inflammatory activity of hop extract, machine learning was combined to chemical and biological characterization of chromatographic hop fractions. In a proof-of-concept study, an extract of hops was fractionated by column chromatography and 40 crude fractions were analyzed by high-throughput loop-injection mass spectrometry. The anti-inflammatory activity of the fractions was measured in a cell-based assay. By using ElasticNet regularized regression, a machine learning technique suitable for solving problems in which the number of parameters (extract compounds) exceeds by far the number of samples (chromatographic fractions), relationships between fluctuations in bioactivity and relative concentrations of compounds across the fractions were examined to detect and rank bioactive principles. Out of a list of >400 m/z values generated by mass spectrometry analysis of the chromatographic fractions, ElasticNet analysis revealed that the m/z value of the prenylated polyphenol, xanthohumol, represented one of the most active principles in the extract. In addition, structures were detected and assigned to related prenylated flavonoids by querying the Global Natural Products Social Molecular Networking (GNPS) tool. Their computational approach adequately performs to identify active principles in crude plant extracts without reliance on bioactivity-guided fractionation.

3.4. Polyphenols and Functional Food Creation

The characterization of the phenolic composition of Bulgarian oil-bearing rose (*Rosa damascena* Mill) was conducted.[99] Bulgaria has a leading role in rose oil processing and the latter is a highly prized product used in perfumery, cosmetics, and pharmaceutics. The enhancement of polyphenols recovery was done using an enzyme-assisted extraction, an environmentally friendly technique, studied as a potential alternative to the conventional organic solvent. Different applications of the extracts in food industry were also shown. An optimization of the enzyme preparation mixture was performed, followed by optimization of the process parameters. Due to the complex composition of the cell wall, effective enzymatic hydrolysis requires the combined use of pectinolytic, cellulolytic and hemicellulolytic activities and the three-component (1:1:1 ratio) enzyme mixture extracted the highest content of total polyphenols, reaching a 43% higher value compared to the non-enzymatically treated sample. Following the green technology approach, membrane separation process was applied for partial concentration of the rose petal extracts due to its advantages such as gentle product treatment and low energy consumption. Using ultra-high performance liquid chromatography coupled to mass spectrometry (UHPLC-MS), nine quercetin and four kaempferol glycosides were identified in the rose petal extract. Galloylquinic acid and ellagitannins have not been described before in *Rosa damascena*. Focusing on the applications of rose petal polyphenols, functional fruit juice beverages were developed. The increase in the half-life of anthocyanins -1.8 times in strawberry juice drink due to the addition of rose extract is an indication of enhancing the pigment stability. The addition of rose petal extract has positive effect on the color quality also in meat processing and can be used successfully for production of sausages with 50% reduced nitrite content, thus meeting the growing consumer demand for substitution of synthetic food additives by natural alternatives.[100]

Rosa damascena polyphenols extracts were also used in nanotechnology for the “green” synthesis of metal nanoparticles. As electrochemical sensing systems provide opportunity for accurate, highly sensitive and susceptible to automatization analysis, utilization of rose oil industry waste for “green” synthesis of nanoparticles and their application for development of modified electrodes for amperometric sensing of hydrogen peroxide (H_2O_2) and vanillin was demonstrated.[101]

The impact of green tea polyphenol fortification of yogurt was also studied. Polyphenol incorporation enhanced the firmness and cohesiveness of yogurt. Moreover, the bioaccessibility of PP was enhanced and their antioxidant capacity preserved after a simulated in vitro digestion, compared to the control sample. Fortified yogurt is therefore suggested to be a suitable dairy product as a bioactive functional food.[102]

Grape pomace polyphenol-rich powder was also used as a flour substitute to fortify wheat bread. It enhanced the tenacity of the dough and increased its antioxidant properties. Grape pomaces were therefore suggested as an appealing ingredient for bread fortification to enhance the positive impact on human health.[103]

4. Polyphenols and Skin Health: Anti-UV, Antiaging, Wound Healing, and Skin Beneficial Impacts of Polyphenols

Besides their interaction with the microbiota and their implication in the metabolism and human health, polyphenols found many applications in the cosmetic fields due to their anti-UV, antiaging, skin lightening, and wound healing properties. They were shown to protect against solar radiation Ultraviolet A (UVA) and Ultraviolet B (UVB) capable of inducing skin cancer, to induce anti-inflammatory and antimicrobial actions, to control melanin pigmentation, and to protect against polluted environment.[104] The beneficial action of PP on sunburn is due to the fact that they act as antioxidants by scavenging the reactive oxygen and nitrogen species responsible for cellular damage.[106,107]

4.1. Design of a Bioinspired Product for Cosmetic Formulation

The possibility to exploit eumelanins, the dark variant of skin pigments that are well known to play a photoprotective role in skin, was studied. These pigments were shown to be endowed with a remarkable antioxidant activity that was ascribed to pigment components derived from the biosynthetic precursor 5,6-dihydroxyindole-2-carboxylic acid (DHICA).[108,109] However, applications in the dermo-cosmetic field have so far been limited by the unfavorable properties of DHICA melanin. To overcome this limitation, a melanin-like polyphenol polymer was prepared by oxidation of methyl ester of DHICA, methyl ester of 5,6-dihydroxyindole-2-carboxylic acid (MeDHICA), under biomimetic conditions. Such pigment exhibited a more favorable solubility profile in hydroalcoholic media and organic solvents (DMSO) that allowed evaluation by chemical tests and cellular models.[109] MeDHICA pigment performed very well in antioxidant assays and proved to be able to prevent reactive oxygen species (ROS) accumulation in UVA-irradiated keratinocytes.[110] These results point to the potential of MeDHICA pigment in dermo-cosmetic formulations as anti-inflammatory and photoprotective ingredient and open new perspectives in the design and applications of bioinspired products.

4.2. Effect of Polyphenols on Skin Hyperpigmentation

The tyrosinase inhibition properties of natural and synthetic polyphenols have been recently reviewed.[111] Several skin pigmentary disorders are associated with the overproduction of melanin as the result of an abnormal function of melanocytes. One of the most common approaches for the control of skin pigmentation involves the inhibition of tyrosinase, a copper-containing enzyme that catalyzes the key steps of melanogenesis.[112] Many PP are able to act as inhibitors of this enzyme, among which particular attention was paid to flavonoids, mostly chalcones, followed by hydroxystilbenes (resveratrol and derivatives). More complex polyphenols isolated from a variety of sources, such as plants belonging to the *Moraceae* family, were also studied. The tyrosinase inhibition properties of synthetic derivatives of natural PP, such as hydroxycinnamic acid and chalcones, have also been reported.[111]

A recently conducted clinical trial showed that a dermocosmetic formulation enriched with 0.5% olive extract containing hydroxytyrosol was among the most efficient skin lightening formulas.[113]

The efficiency of PP on the skin was not only shown through cutaneous administration, but also through oral administration.

As an example, a recent clinical trial showed that a 12-week administration of apple polyphenol (procyanidins) tablets (300 or 600 mg day^{-1}) is able to prevent UV-induced skin pigmentation.[114] Since several studies demonstrated that procyanidins may induce a change in the gut microbiota composition and that modulation of the gut microbiome can influence skin homeostasis pathways to counteract UV damage, the suppression of pigmentation by apple polyphenols could in part be mediated by the gut microbiota.[115–117]

4.3. Effect of Incorporation in Carrier Systems on Polyphenols Efficacy

In recent years, extensive research has been devoted to studying novel strategies for the enhancement of polyphenols activity through the incorporation in innovative carrier systems to be administered by different routes. Nanosized delivery systems, such as phospholipid vesicles, were investigated with the purpose of increasing the efficacy of polyphenols by protecting them from degradation, enhancing their solubility and bioavailability, and delivering adequate concentrations to the target site in a controlled manner.

Phospholipid vesicles are the most widely used platform for marketed pharmaceutical/nutraceutical products, as well as the best-investigated platform in clinical trials and academic research. However, clinical translation of these systems is often impeded by the scalability of the formulations. Indeed, the latter can be problematic to manufacture on a large scale, at a high level of quality, with batch-to-batch reproducibility, and to remain stable after the manufacturing process, during long-term storage and upon clinical administration. Hence, a balance between the complexity of the formulation design, the therapeutic efficacy and the clinical translation is needed.

Phospholipid vesicles can be prepared by the conventional thin film hydration method or, as described more recently, by the direct sonication of phospholipids in aqueous medium in the presence of a polyphenol. This method is more rapid, easier, and more biocompatible, as it does not involve the use of organic solvents.

Phospholipid vesicles are generally characterized in terms of physicochemical and technological features, such as average size, charge, morphology, long-term stability, entrapment efficiency, and release profile. Further, given the well-recognized beneficial effects of polyphenols on human health (i.e., antioxidant, anti-inflammatory, anticarcinogenic), both in vitro and in vivo tests are usually performed to assess the bioactivity of the payload delivered by the vesicles. Results have shown that the bioefficacy can be amplified, while side effects and toxicity are prevented or reduced.

Both raw polyphenols and extracts composed of different polyphenol classes have been successfully loaded in phospholipid vesicles, mostly intended for topical applications. Among polyphenols, quercetin and resveratrol have received an increasing scientific attention, leading to investigations on their biological activities and to numerous publications. They have been loaded in phospholipid vesicles, which have been characterized for the main physico-chemical properties, the antioxidant power, along with in vitro cytotoxicity and uptake in skin cells, activity against reactive oxygen species (ROS), and in vivo anti-inflammatory and wound healing efficacy. The polyphenol-loaded vesicles have shown small size (~100 nm), good homogeneity, spherical, uni- or oligolamellar morphology, good stability during storage, strong antioxidant activity, biocompatibility with skin cells and scavenging activity towards ROS, amelioration of skin lesions with reduction of oedema and leukocyte infiltration.[116–118]

Considering these findings, polyphenol vesicular formulations may be of value in the treatment of different skin conditions associated with inflammation and oxidative stress.

5. Conclusion

During the past three decades, the scientific community has experienced a tremendous increase in research activities to decipher the multiple roles that polyphenols play in foods and in human beings. Their diverse biological activities render polyphenols valuable natural products for various industrial applications. Whether recovered from foods or from agricultural side streams, innovative technologies are increasingly used to retain their bioactivities. Thanks to their demonstrated antioxidative, antiradical, anti-inflammatory properties and many other activities, studies on PP unveiled favorable and encouraging in vitro and in vivo effects. Through specific modes of action, they exhibit high neuroprotective efficiency and healthy aging aspects by fighting against oxidative stress. PP metabolites were shown to interact with mitochondria and gut microbiota to combat many diseases such as obesity, depression, inflammation, and allergy. Due to their skin lightening, antiaging, wound healing, and UV-protective properties, PP were also suggested to be used as active ingredients in the cosmetic industry. Furthermore, incorporation of PP in different food industries opened the way for functional foods creation, offering a beneficial antioxidant added value to the enriched end products. A broad range of studies is increasingly supporting the positive effects of PP on human health.

More research advances will contribute to draw a clear picture of the crucial implication of polyphenol metabolites. Their testing in clinical trials will pave the way to a better understanding of their mechanisms of action. Whether used in cosmetics, nutraceuticals or pharmaceuticals, defining and depicting pivotal bioactivities of polyphenols will definitely highlight their strategic role in disease prevention as a complementary approach. We strongly believe that polyphenols and metabolites in our food will strongly determine our health and longevity.

There is not much information in clinical aspects or doses evaluated at human level. As well, independently of the dose applied, also an integrative evaluation is necessary including bioaccessibility and microbiota effects. It may be possible, for example, that some compounds show low bioaccessibility, hence we will need a higher dose but probably the microbiota can liberate the phenolics in a next step of digestion allowing to have the desired effect.

Recently, human studies have been published that address the relationship between fruit intake and the contribution of the microbiota to the metabolism of polyphenols.[120–124] However, one is only beginning to understand the relationships. For example, specific blood and urine metabolic biomarkers of apple polyphenol intake and putative associations with specific genera of fecal bacteria have been identified.[125] The authors conclude that the associations need to be confirmed in specifically designed mechanistic studies, which is true for most of the clinical trials on this issue published to date.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data available on request from the authors.

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