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Phenolic compounds: current industrial applications, limitations and future challenges

Bianca R. Albuquerque, [a,b] Sandrina A. Heleno, *[a] M. Beatriz P. P. Oliveira, [b] Lillian Barros *[a] and Isabel C. F. R. Ferreira [a]

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Phenolic compounds are natural bioactive molecules found mainly in plant tissues that have shown interesting bioactivities, such as antioxidant, antimicrobial, anti-inflammatory, and antiproliferative activities, among others, which has led to great interest in their use by several industries. However, despite the large number of scientific studies on this topic, some issues still need to be studied and solved, such as the understanding of the main actions of these compounds in organisms. Besides their large potential applicability in industry, phenolic compounds still face some issues making it necessary to develop strategies to improve bioavailability, sustainable technologies of extraction and refinement, and stability procedures to increase the range of applicability. This review focuses on the most recent advances in the applications of phenolic compounds in different technological and medicinal areas. In addition, techniques to improve their sustainable resourcing, stability and bioavailability will be presented and discussed.

1. Introduction

Nowadays, phenolic compounds (PC) are one of the classes of bioactive molecules most studied by the scientific community; these molecules have well-reported health benefits; a daily diet enriched in these compounds is important to promote well-being. PC are considered antioxidants due to the donation of a hydrogen atom and/or an electron to free radicals, causing the break of chain reaction of oxidation. The antioxidant effect depends on the number and position of the hydroxyl groups.[1] In organisms, an oxidative process can be responsible for the generation of free radicals that attack the cells, leading to serious diseases, such as cancer, cardiovascular diseases, atherosclerosis, neurological disorders, hypertension, and diabetes mellitus, due to oxidative and nitrosative stress.[1,2] Other important bioactivities for maintaining good health have also been associated with these compounds, *e.g.* anti-inflammatory, antimicrobial, and anti-proliferative activities;[1–3] these biological activities have aroused interest in the use of these molecules in the formulation of nutraceutical products.[1,2] However, although many bioactivities of PC are proven *in vitro*, there is still a lack of information on their action *in vivo*; this is crucial information since several factors, such as bioavailability and absorption of these compounds, can interfere with their bioactive action.[1,4]

In addition to the pharmacological interest in these compounds, their biological activities have also been explored in other industry sectors, such as in the food,[1,5,6] in the cosmetic[3,7] and in the packaging and textile industries.[8,9]

This review presents a detailed description regarding the applications and limitations of PC in industry, aiming to create a future perspective for studies and practical use of these compounds.

2. Phenolic compounds

PC are the main substances formed by the secondary metabolism of plants. They are responsible for pigmentation and astringency and also act as protective agents against UV light, besides protecting the plants against parasites and insects.[1,2] These compounds can be found in a huge diversity of matrices, such as fruits and vegetables, among others (Table 1).

Another important approach is obtaining PC from residues and byproducts of the food production chain, since it is a cheap natural source of these compounds, and has no economic value, contributing to the reduction of waste, because agri-food bioresidues represent a significant percentage in the food processing industries. For example, wine making residues correspond to 20%–30% (w/w) of the total processed grapes

[a]*Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal. E-mail: lillian@ipb.pt, sheleno@ipb.pt; Tel: +351-273-303285, +351-273-303285*
[b]*REQUIMTE – Science Chemical Department, Faculty of Pharmacy, University of Porto, Rua Jorge Viterbo Ferreira no. 228, 4050-313 Porto, Portugal*

Table 1 Bioactive properties of the phenolic compounds

Phenolic compound	Main sources	Bioactivities	Ref.
Phenolic acids			
Hydroxybenzoic acids			
Sinapic acid	Berries, rye, mustard and vegetables	Antioxidant, anti-inflammatory, antimicrobial, and anticancer activities.	69
Ellagic acid	Berries	Antioxidant, anti-inflammatory, and antitumoral activities.	2
Gallic acid	Grapes, tea and wine	Antioxidant, antimicrobial, anti-inflammatory, antitumoral, and neuroprotective activities.	12 and 37
Hydroxycinnamic acids			
Ferulic acid	Cereal grains, fruits, mushrooms and rice	Antioxidant, antitumoral, antimicrobial, and antidiabetic activities.	12
Caffeic acid	Coffee, mushrooms and propolis	Antioxidant, antimicrobial, anti-inflammatory, antiviral, and antitumoral activities.	12
p-Coumaric acid	Carrot, coffee, garlic, grapes, spinach and tomatoes	Antioxidant, antimicrobial, antiviral, antitumoral, anti-inflammatory and neuroprotective activities.	12 and 15
Flavonoids			
Flavonols			
Kaempferol	Cabbage, cauliflower, propolis and spinach	Antioxidant, anti-inflammatory, antitumoral, and cardioprotective activities.	2
Myricetin and derivatives	Berries, herbs and vegetables	Antioxidant, anti-inflammatory, and antitumoral activities.	70
Quercetin and derivatives	Apples, berries, onion and pears	Antioxidant, anti-inflammatory, antitumoral, and cardioprotective activities.	2
Flavones			
Apigenin	Fruits and vegetables	Antioxidant, anti-inflammatory, antiviral, antiproliferative, and antitumoral activities.	2
Tangeretin	Citrus fruits	Anti-inflammatory, antiproliferative, and antitumoral activities.	71
Baicalein	*Scutellaria Baicalensis* Georg	Antioxidant, anti-inflammatory, and neuroprotective activities.	72 and 73
Luteolin	Broccoli, celery and green peppers	Antioxidant, anti-inflammatory, and antitumoral activities.	2 and 25
Flavanols			
Catechin	Berries, cacao and green tea	Antioxidant and antimicrobial activities.	2
Epicatechin gallate, epigallocatechin, and epigallocatechin gallate	Berries, cacao, grapes and green tea	Anti-inflammatory, anti-obesity, and cardioprotective activities.	2
Flavanones			
Hesperidin	Citrus fruits	Antioxidant, anti-inflammatory, antitumoral, and antiallergic activities.	1 and 74
Naringin	Citrus fruits and grapefruit	Antioxidant, anti-inflammatory, anticancer, anti-lipidemic, and antibacterial activities.	2 and 24
Taxifolin	Bark (genus *Pinus* or *Larix*) and seeds (genus *Silybum*)	Antioxidant, anti-inflammatory, antiviral, and antibacterial activities, and anticancer, neuroprotective activities.	75
Isoflavones	Soybeans and soyproducts	Cardioprotective activity, estrogenic effects.	2
Anthocyanins	Berries, grapes and purple carrot	Antimicrobial, anti-inflammatory, antioxidant, anti-proliferative, and cardioprotective activities.	2
Tannins			
Epigallocatechin gallate Gallotannin	Apples, berries and cacao	Antioxidant, antimicrobial, and antitumoral activities.	1
Stilbenes			
Resveratrol	Berries, grapes and peanuts	Antioxidant, anti-inflammatory, and cardioprotective activities.	2
Lignans	Flaxseed and sesame	Antioxidant, anticancer, anti-inflammatory, neuroprotective, and antimicrobial activities.	2 and 6

and around 70% of grape polyphenols remain in the pomace.[3] Other examples are pomegranate (*Punica granatum* L.) peels rich in PC, which correspond to up to 40% of the whole fruit; however they are usually considered as waste;[10] and anthocyanins can also be obtained from pomace and peel discarded from juice, jam and wine production.[3,11]

In terms of chemical features, PC are formed by one or more aromatic rings bonded to one or more hydroxyl groups,[2,6] resulting in different chemical structures; these compounds are divided into different groups: phenolic acids, flavonoids, tannins, stilbenes and lignans.[1,4]

2.1. Phenolic acids

Phenolic acids represent the simplest class of PC; their basic structure contains one phenolic ring and a carboxylic acid function, and, according to their carbon skeleton, they are divided into two groups: (i) hydroxybenzoic acids (C6–C1) that are derived from benzoic acid and (ii) hydroxycinnamic acids (C6–C3) that are derived from cinnamic acid (Fig. 1A.1).[2,12] The last one is composed of the most common phenolic acids, such as caffeic and ferulic acids,[2,12] found in vegetables, fruits and grains as presented in Table 1. In general, these compounds have several important bioactivities (Table 1).

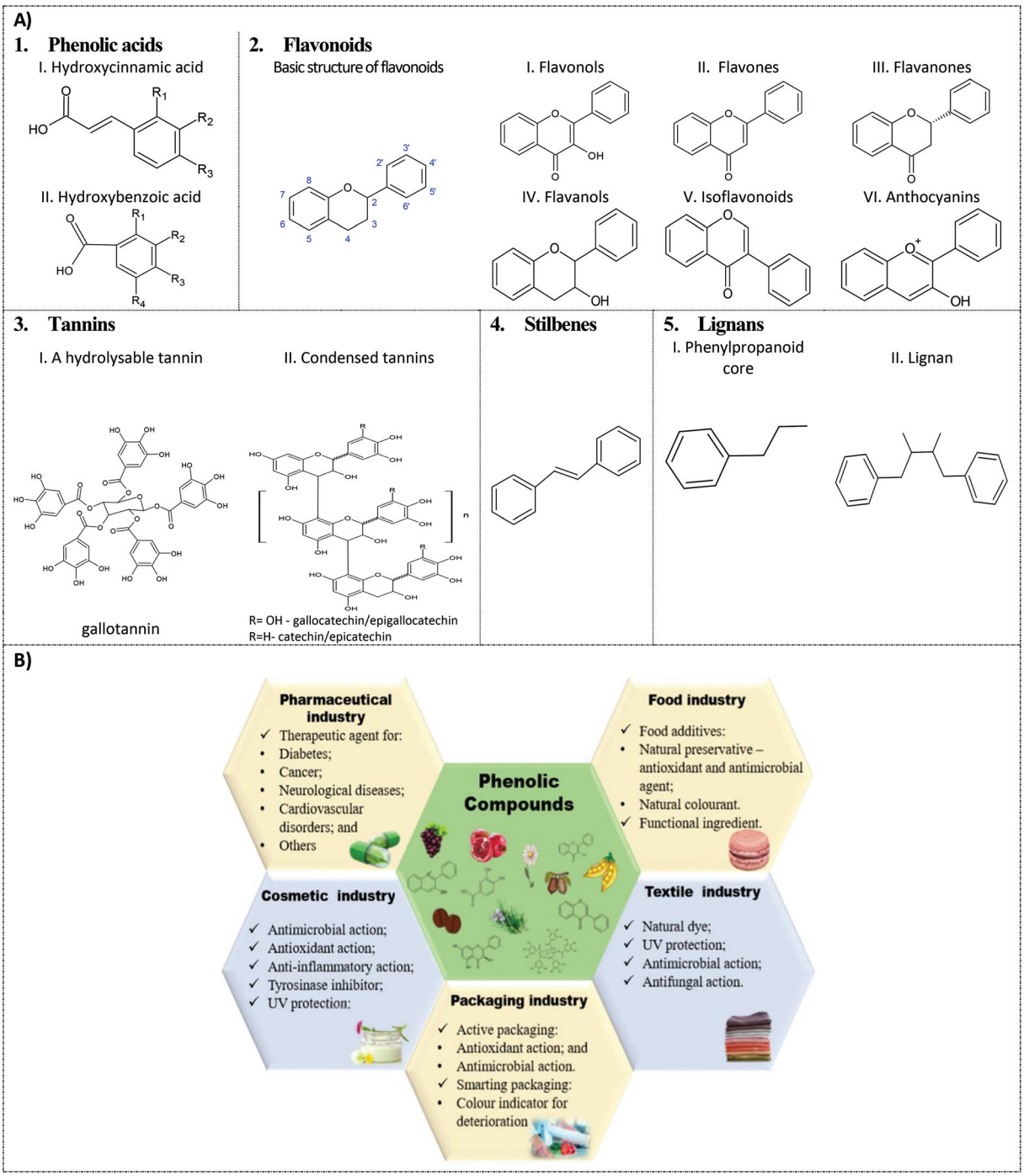

Fig. 1 Main phenolic compounds and their industrial application. (A) Chemical structures. (B) Industrial applications.

2.2. Flavonoids

Flavonoids are the most abundant PC, with more than 8000 compounds. Their basic structure consists of fifteen carbon atoms (C6–C3–C6), which are built in two benzene rings (A and B), linked by a heterocyclic pyrane ring (C) (Fig. 1A.2). According to the bond between B and C rings and the substitution patterns of the C ring, they are divided into six different sub-groups: flavonols, flavones, flavonones, flavanols, isoflavonoids and anthocyanins.[2,6] This class of compounds is widespread in several food matrices and is highly investigated for their diverse bioactivities (Table 1). Regarding their antioxidant capacity, the configuration, substitution and the number of hydroxyl groups are substantially responsible for giving this bioactivity to these compounds.[2,6]

2.2.1 Flavonols. Flavonols are flavonoids with a double bond between C2 and C3, with a hydroxyl group attached at the C3 and a carboxyl group at C4 (Fig. 1A.2I); this configuration has three functional groups available to exercise their reaction with other substances.[2,6] These flavonoids are found in many edible and medicinal plants, being highly investigated due to their multiple bioactivities (Table 1). Among this group, the most known compounds are kaempferol, myricetin, quercetin and their respective derivatives of quercetin.[2]

2.2.2 Flavones. Flavones have a double bond between C2 and C3, with a structure similar to flavonols, but with the absence of a hydroxyl group at C3 (Fig. 1A.2II). Some flavones and their respective sources and bioactivities can be found in Table 1. Luteolin and apigenin are the most abundant flavones; the presence of free hydroxyl groups in their rings A and B is responsible for their antioxidant activity.[2,6]

2.2.3 Flavanones. There are more than 160 types of flavanones belonging to 36 plant families, being also precursors of many other flavonoids.[2,6] These compounds are chemically characterized by containing a carboxyl group at position 4, without the presence of a double bond between C2 and C3 (Fig. 1A.2III).[2] Flavanones are mainly found in citrus fruits (Table 1). Among this class of compounds, naringenin and hesperidin are the most investigated.[2,6]

2.2.4 Flavanols. Flavanols, also known as flavan-3-ols, are the largest sub-group of flavonoids. This class is characterized only by the presence of a functional hydroxyl group at position 3 (Fig. 1A.2IV).[2,6] The major compounds of this class are catechin and epicatechins.[2] Flavan-3-ols can be found in several fruits and plants (Table 1). Among these sources, green tea (*Camellia sinensis* L.) stands out for the high concentration of these compounds in its composition, and, due to the bioactivities of flavan-3-ols, the ingestion of this tea has been associated with low incidence of chronic cardiovascular disease.[1,2]

2.2.5 Isoflavonoids. Isoflavonoids are the only flavonoids that have the benzenoid substituent at position 3 (Fig. 1A.2V), which gives them a structure similar to endogenous estrogens, making them capable of displaying agonistic and anti-agonistic interactions with estrogen receptors.[2,6] More than 2000 isoflavonoids have been identified, of which isoflavones are the most known;[2] this compound shows interesting bioactivities (Table 1).

2.2.6 Anthocyanins. Anthocyanins are derived from flavonols that have a hydroxyl group at position 3. In addition they have two double bonds (one between the oxygen atom and carbon and the other one between carbon 3 and 4), and there is a lack of a ketone oxygen at position 4 (Fig. 1A.2VI); therefore its structure is basically described as being a flavylium ion.[2,6] Anthocyanins are responsible for the colour of several red-purple fruits, vegetables and flowers. Aglycone anthocyanins are denoted as anthocyanidins; in nature there are 17 natural anthocyanidins, and cyanidin, delphinidin, petunidin, peonidin, pelargonidin and malvidin are the most common species.[5] In Table 1 are presented the main sources and bioactivities of these PC. In addition to their interesting health beneficial bioactivities, anthocyanins have been used as natural colourants, especially by the food industry.[1,5]

2.3. Tannins

Tannins are the major phenolic polymers found in plant tissues. These molecules are known to confer astringent and bitter taste to some fruits (*e.g.* in Table 1). Tannins are complex phenolics that are divided into two subclasses: hydrolysable tannins and condensed tannins. Hydrolysable tannins are blends of simple phenols, *e.g.* ellagic and gallic acids, with a carbohydrate. When subjected to acid or basic conditions, these compounds can be hydrolysed producing phenolic acids and carbohydrate molecules; an example is a hydrolysed tannin structure formed from gallic acid (gallotannin)[2] (Fig. 1A.3I). Condensed tannins are formed by condensing two or more monomers of flavan-3-ol units, linked together mostly by bonds between the A rings of the flavanol units and the pyran rings of other flavanols[2] (Fig. 1A.3II). Regarding bioactive potential, tannins are little investigated, probably due to the complexity of their structure; however, in the last few years, proanthocyanidins have attracted attention due to their health benefits.[2]

2.4. Stilbenes

Stilbenes are characterized by the chemical structure C6–C2–C6, with two benzene rings connected by a double bond (Fig. 1A.4).[2,6] According to the central double bond, they are divided into the isomers *Z* and *E*; changing the isomerization type generally decreases its biological activity.[2] There are more than 400 stilbenes known; however, the presence of these substances is limited to plant families that have the key enzyme involved in stilbene biosynthesis.[1] Resveratrol is one of the most known stilbenes; and due to its bioactivities (Table 1), this compound has been widely studied.[2,6]

2.5. Lignans

Lignans are secondary plant metabolites exhibiting different chemical structures; however, the basic structure is composed of the combination of phenylpropanoid dimers (C6–C3, Fig. 1A.5I) linked by the central carbons of the side chains (Fig. 1A.5II).[2] This class of PC is present in some seeds (Table 1). Lignans have estrogenic and anti-estrogenic activities,[1] in addition to other bioactivities (Table 1).

3. Phenolic compounds as potential pharmaceutical agents

PC are bioactive compounds that are normally associated with protective action for maintaining good health when consumed in the regular diet. These compounds have showed inhibitory action against the evolution of several serious diseases, such as cancer, Alzheimer's, and diabetes, among others.[1,2] These beneficial effects have been attributed mainly to the antioxidant and radical scavenging activities that can delay or

Table 2 Phenolic compounds used for treatment and prevention of diseases

Phenolic compounds	Health disorder	Type of assay	Effects	Ref.
Phenolic acids				
Ellagic acid	Skeletal muscle ischemia/ reperfusion injury	Animal model	Treatment attenuated the muscle damage reducing lipid peroxidation levels.	74
Gallic acid	Type 2 diabetes	Animal model	Improved glucose tolerance, decreased brain oxidative stress and inflammation, and inhibited hippocampal apoptosis.	15
p-Coumaric acid	Type 2 diabetes	Animal model		
Sinapic acid	Cataract	Animal model	Increased the content of reduced glutathione in the lenses of rats in the early phase of estrogenic deficiency.	76
	Bone loss	Animal model	Increased bone formation.	69
Flavonoids				
Anthocyanins	Mild-to-moderate dementia	Clinical trial	Improvement in verbal fluency, and in short- and long-term memory.	20
	Type 2 diabetes	Clinical trial	Reduction in elevated blood glucose levels.	14
	Hypercholesterolemia	Clinical trial	Decrease in serum low-density lipoprotein-cholesterol (LDL).	19
	Melanoma	Animal model	Inhibited tumour growth, lung metastasis and tumour-angiogenesis.	23
Baicalein	Ischemic stroke	Animal model	Reduced neurobehavioral deficits and brain infarct volume.	72
	Temporal lobe epilepsy	Animal model	Improved cognitive behaviour and memory in rats.	73
Catechin	Dry eye disease	Animal model	Increased tear production, conjunctival goblet cells and anti-inflammatory activity.	77
Epigallocatechin gallate	Diabetic nephropathy	Clinical trial	Reduced the urinary albumin-creatinine ratio by 41%.	78
Hesperidin	Skeletal muscle ischemia/ reperfusion injury	Animal model	Decreased muscle damage by reducing lipid peroxidation levels.	74
Isoflavones	High blood pressure	Clinical trial	Decreased blood pressure of hypertensive.	18
Luteolin	Lung cancer	Animal model	Positive effect synergetic with tumour necrosis factor-related apoptosis-inducing ligand (TRAIL).	25
Kaempferol	Breast cancer	Animal model	Inhibition of the growth of breast carcinoma.	22
Myricetin	Colonic chronic inflammation	Animal model	Prevention of the incidence of colorectal tumorigenesis and reduction in the size of colorectal polyps.	70
Naringin	Oesophageal cancer	Animal model	Reduced approximately 30% of the tumour size.	24
Quercetin	Neurodegenerative diseases	Animal model	Improved learning and memory of rats.	21
	Cardiovascular disease	Clinical trial	Increased brachial arterial diameter exerting acute vasodilator.	16
	Polycystic ovary syndrome	Clinical trial	Improvement in adiponectin-mediated insulin resistance and hormonal profile of women with polycystic ovary syndrome.	79
Lignans	Glaucoma	Animal model	Improvement in response to oxidative stress in retinal ganglion cells and retinas of glaucomatous rats.	80
Resveratrol	Cardiovascular disease	Clinical trial	Decreased LDL level and protection against unfavourable hemorheological changes.	17
	Type 2 diabetes	Clinical trial	Significant effects in the antioxidant activity in the blood and weight loss of diabetic subjects.	13
Tangeretin	Colorectal cancer	Animal model	Reduction in tumour incidence, multiplicity and pathological signs of colorectal adenoma.	71

inhibit the oxidation of DNA, proteins and lipids.[1,2,6] This review introduces some scientific studies (Table 2) that prove the efficacy of PC as pharmaceutical agents in alternative or in synergism with aggressive treatments of diverse ailments.

Diabetes, for instance, is a chronic disease that affects a significant portion of population; the number of diabetic patients has been growing year by year. In 2030, it is estimated that at least 400 million of people will be diagnosed with diabetes disorder. Oxidative stress has been indicated as a precursor of diabetes disorder; in fact, the reactive oxygen species (ROS) that are not neutralized lead to inflammatory conditions in the body; thus, the antioxidant action of PC has been studied in the treatment of diabetes.[2,13–15] Anthocyanins have showed an inhibitory action against the α-amylase and α-glucosidase enzymes, which leads to a reduction in the hydrolysis of carbohydrates in monosaccharides, thus hindering their absorption.[14] In diabetic mice, supplementation with anthocyanin-rich lowbush blueberry extract (500 mg per wb) or with malvidin-3-*O*-glycoside (300 mg per wb) showed high reduction in blood glucose levels compared with the known anti-diabetic drug, metformin (27%, 300 mg per wb).[14] In diabetic subjects, the daily consumption of resveratrol (800 mg day^{-1}) has been sufficient to increase the antioxidant capacity of the blood, in addition to contributing positively to other health parameters, such as the decrease in blood pressure, weight and body mass index (BMI) of the patients.[13]

Cardiovascular diseases (CVD) are highly associated with dietary habits; thus, a diet based on fruits, cereals and vegetables is recommended to prevent CVD.[2] Some PC have showed cardioprotective action due to their bioactive properties, namely being a potential vasodilator, with antiplatelets and ability to reduce blood pressure and LDL-cholesterol.[2,16–19] For instance, the treatment with resveratrol (10 mg day^{-1} for 3 months) improved left ventricle diastolic function, endothelial function, lowered the LDL-cholesterol level and protected against unfavorable hemorheological changes measured in post-infarction patients;[17] and quercetin administered in a unique dose (400 mg) promoted vasodilatation in healthy humans.[16] For hypertensive patients, the ingestion of 65–153 mg of soy isoflavones per day (1–12 months) had an effect on lowering blood pressure.[18]

Several studies demonstrated that PC possess neuroprotective action (Table 2); anthocyanins, for instance, have shown ability to improve cognitive function lost by aging.[20] The diary supplementation with anthocyanin-rich cherry juice (200 mL day^{-1}) can lead to significant recuperation of dementia.[20] Also, regarding the flavonoids, the administration of quercetin conjugated with superparamagnetic iron oxide nanoparticles (50–100 mg kg^{-1}) to rats was able to improve the animal's learning capacity and memory.[21]

The search for alternative therapeutics has led to numerous studies to evaluate the anticancer activity of PC against diverse tumour cell lines.[1,2] PC have showed ability to inhibit the growth of different tumours; for instance, the flavonoids kaempferol, naringin and anthocyanins have significant activity on melanoma, oesophageal and breast carcinomas, respectively.[22–24] Positive synergetic effects have also been detected with combined use of traditional therapeutic medicine and PC. For instance, luteolin has showed a synergetic effect when used with tumour necrosis factor-related apoptosis-inducing ligand (TRIAL) in the treatment of lung cancer, potentiating the effect of the drug in inhibiting tumour growth and increased apoptotic cell death.[25] Similar synergetic effects were found in the combined use of doxorubicin, a chemotherapy drug, with naringin or orange-peel extract to treat oesophageal cancer in mice.[24]

4. Phenolic compounds: industrial application

PC have several biotechnological applications in different industries (Fig. 1B). Their exploitation is mainly due to their antioxidant, antimicrobial, and colouring properties, among others, especially explored for food preservation, by the food and packing industries, and in the cosmetics and also the textile industries.

4.1. Food industry

Facing the restrictions to the use of artificial food additives, the scientific community has been working on the development of natural alternatives.

The antioxidant and antimicrobial activities of PC exhibited by plant extracts have been crucial to the application of these compounds as preservatives, thus increasing the shelf-life of several foodstuffs. In Table 3, some practical applications of natural preservative additives are presented. For instance, the addition of phenolic extract obtained from *Litchi chinensis* Sonn. pericarp into sheep meat nuggets had similar inhibition of the lipid peroxidation to the one revealed by the synthetic antioxidant BHT (butylated hydroxyl toluene).[26] Also, despite the degradation of PC with high temperature, the use of pheno-

Table 3 Applications of phenolic compounds in the food industry

Phenolic compounds	Source	Product	Effects	Ref.
Food Additives				
Phenolic extracts	*Matricaria recutita* L. *Foeniculum vulgare* Mill.	Yogurt	Antioxidant activity.	28
	Olive live mill water	Olive oil for the frying process of French fries	Preventing the deterioration of α-tocopherol and reducing the formation of acrolein and hexanal.	27
	Litchi chinensis Sonn.	Sheep meat nuggets	Antioxidant activity.	26
	Rosmarinus officinalis L.	Cottage cheese	Antioxidant activity.	31
	Punica granatum L. peel	Ice cream	Antioxidant and α-glucosidase activities.	10
	Camellia sinensis L.	Bread	Fortification with bioactive polyphenols.	32
Hydroxycitric acid	*Garcinia cowa* Roxb. ex DC rind	Pasta	Antioxidant activity and improvement of sensory quality.	53
Taxifolin	Commercial compound	Apple juice	Fortification with bioactive molecules.	63
Anthocyanins	*Euterpe edulis* M.	Fermented and unfermented beverages	Improvement of the colour.	51
	Phaseolus vulgaris L.	Sport beverage	Stable colour and fortification with bioactive molecules.	56
	Myrciaria cauliflora Mart.	Fresh sausage	Improvement of colour, antioxidant and antimicrobial activities.	30
	Prunus nepalensis L.	Yoghurt, syrup and hard-boiled candy	Stable colour and sensory acceptance.	29
Catechin and epigallocatechin gallate	*Camellia sinensis* L.	Low-fat hard cheese	Antioxidant activity.	62

lic extract obtained from *Olea europaea* L. residues in oil reduced the oxidation caused by a frying process (180 °C) in the production of French fries and preserved the vitamins (tocopherols) of oil used in the process for 6 hours, reduced the formation of unwanted compounds (acrolein and hexanal), and in contrast to the use of BHT as an antioxidant, promoted the production of acrylamide, which shows the advantage of these natural molecules in relation to artificial compounds.[27] Higher protection against oxidative processes was also observed with the used PC obtained from *Matricaria recutita* L. and *Foeniculum vulgare* Mill. in comparison with potassium sorbate when added in the same concentration into yogurt; *e.g.* EC_{50} values to DPPH scavenging activity yogurts fortified with plant extracts were 45 and 94 mg mL^{-1}, respectively, while the synthetic antioxidant showed an EC_{50} of 111 mg mL^{-1}.[28]

Anthocyanins are PC that provide attractive red-purple coloration to plant tissues; their use as a colouring additive is allowed by EFSA under code E163; however technological limitations, such as low stability and photodegradation, are some barriers to their industrial use.[5] In contrast, satisfactory results have been obtained with the application of anthocyanins as colorants in several types of products (Table 3); for example anthocyanins from *Prunus nepalensis* L. added in high concentration into foods produced under different conditions, such as yoghurt, syrup and hard boiled candies, showed stable colour and improved the sensory acceptance of these products.[29] In addition to their color capacity, anthocyanins can also provide biological benefits. For example, fresh sausages formulated with 2%–4% microencapsulated anthocyanins from *Myrciaria cauliflora* showed lower microbial degradation and greater antioxidant activity than a similar product formulated with carmine.[30] Despite promising studies emphasizing PC potential as food additives, there is still a long way to their massive industrial application. Several studies are needed to evaluate the safe consumption of these substances and obtain their approval by the regulatory authorities *e.g.* FDA (Food and Drug Administration, in the United States) and EFSA (European Food Safety Authority, in the European Union). Unfortunately, only a limited number of natural additives based on PC are legislated. As far as we know, authorized PC used as food additives include catechin (allowed in the US and EU (E300)) and ferulic acid (in Japan) as antioxidants, and anthocyanins as mentioned before.[5]

PC have also been used in processed foods to enhance their functional properties and provide consumer health benefits. In this context, *Rosmarinus officinalis* L. extract has increased the antioxidant activity in cottage cheese,[31] and *C. sinensis* polyphenols have improved the bioactive profile of bread and cheese,[32,33] and the addition of *P. granatum* extract into ice cream provided functional properties to product, namely antioxidant and α-glucosidase inhibitory activities, without changing its sensory acceptance.[10]

4.2. Cosmetic industry

As well as in the food industry, the cosmetics industry has also been exploiting natural additives as alternatives to the artificial ones.[7,34] In this context, PC have showed potential for use as bioactive ingredients in cosmeceutical products.[3]

PC can absorb ultraviolet radiation due to the presence of chromophores in their structure, avoiding the penetration of solar radiation into the skin. UV protection has been described for some PC, such as quercetin, resveratrol and hydroxycinnamic acids, which presented a sun protection factor (SPF) ranging from 7 to 30.[34]

As is well known, free radicals can lead to early aging due to several interactions that reactive oxygen species can make with proteins of the skin, as well as active enzymes such as collagenase, elastase, and tyrosinase, resulting in the degradation of collagen and elastin. Against these skin lesions, a body cream formulated with phenolic extract of *Nymphaea rubra* Roxb was effective on skin wrinkle reduction and skin whitening with no irritation efficiency in healthy volunteers after 60 days of use; these benefits obtained on the volunteers' skin were correlated with the high antioxidant activity of the extract (IC_{50} 0.075 and 0.273 mg mL^{-1} for DPPH and ABTS assays, respectively) and with its tyrosinase inhibitory activity (IC_{50} = 3.285 mg mL^{-1}).[35]

Hydroxycinnamic acids, namely *p*-hydroxybenzoic, *p*-coumaric, and protocatechuic acids, have showed high stability, for a long time (6 months) when added to a semi-solid base cream and maintain the anti-tyrosinase, anti-inflammatory and antimicrobial activities, making them suitable to be explored as multifunctional cosmeceutical ingredients.[7]

4.3. Packaging industry

Some PC have also been used to elaborate packaging formulations with antioxidant and antimicrobial properties.[9,36] As anthocyanins are PC with interesting colour properties and high antioxidant activity these flavonoids are able to prevent the lipid oxidation of olive oil when added to the packing formulation.[36] Moreover, the colour of anthocyanins depends on the pH, ranging from red (pH ~2) to green (pH ~11), which enable the fabrication of films that are susceptible to pH changes such as the film based on gelatin/polyvinyl alcohol developed with anthocyanins from mulberry (*Morus* sp.) to assess fish spoilage by changing the colour of the packaging from purple (fresh fish) to brown (fish after 18 h), and finally dark green after 24 h.[9] Phenolic acids, namely gallic and caffeic acids, have been used in chitosan-based biofilms to inhibit the growth of *Bacillus subtilis* and *Staphylococcus aureus*, in addition to improving physical characteristics, such as vapor and oxygen permeability of the film.[37] Tannins interact with proteins through hydrogen bonding or non-covalent bonds; this property was explored to develop protein-based biofilms with tannins that have antioxidant and antimicrobial activity against *Escherichia coli* and *Listeria innocua.*[38]

4.4. Textile industry

The textile industry is one of the highest polluters, since high amounts of water are contaminated with a heavy load of chemicals. On the other hand, allergic reactions also have

been associated with synthetic dyes.[8,39] In this scenario, the interest in the use of PC as natural dyes with high biodegradability has grown.[8,39] In addition to being less aggressive to the environment, natural dyes obtained from oak (*Quercus* sp.) bark, mostly composed of gallotannin, ellagitannin, quercetin and quercetin-3-*O*-glucoside, and from red, black and green tea extracts, showed UV protection when applied in Tussah silk and cotton, respectively.[8,39] Antimicrobial activity against *E. coli* and *S. aureus* was also achieved with the use of natural dye from oak bark.[8]

5. Challenges for the use of phenolic compounds by industries

The previous topics showed the potential of the PC for various applications in different industry segments. However, for the practical and viable use of these molecules, some barriers need to be overcome; for example the low concentration of these compounds found in plant tissues can be a limiter to meet their high demand by the industries; also their sensitivity to various environmental factors, such as light and heat, can lead to their degradation and, consequently, the loss of their bioactivities. Furthermore, for efficient use as a therapeutic and functional agent, bioavailability features need to be better understood and improved.

5.1. Sustainable production of phenolic compounds

5.1.1. Elicitation. Elicitation is a technique that causes a stress condition, *e.g.* salinity, nutrient deficiency, excessive radiation (UV), extreme cold or hot temperatures, and the presence of microorganisms, which leads to an increasing production of secondary metabolites in the plants.[40] In Table 4 are presented some studies of the enrichment of phenolics in plants through elicitation. This technique has led to a high increase of the concentration of PC with regard to control plants, such as the case of oxyresveratrol of *Morus alba* L. callus that increased more than 730-fold with the addition of 2-hydroxypropyl-β-cyclodextrin to the culture media.[41] Also, the elicitation technique has showed improvement in the bioactivities of the extract plants, which can be correlated with the enrichment in PC. In a recent study, Złotek *et al.*[40] compared the effect of two abiotic elicitors, arachidonic (AA) and jamonic acids (JA), to increase the phenolic composition and bioactivities of *Triticum aestivum* L. According to the results, the AA elicitation had higher impact on flavone content, while the JA elicitor was more favourable for phenolic acid production. Regarding the bioactivities, higher antioxidant and anti-inflammatory activities were achieved with AA. On the other hand, JA had no positive effect on the lipoxygenase inhibition. A JA derivative, methyl jasmonate, also increased the antioxidant activity of *Allium cepa* L., in addition to its increased quercetin concentration.[42]

Table 4 Alternatives for the sustainable production of phenolic compounds: (1) Plant cell elicitation; and (2) metabolic engineering of microorganisms

Phenolic compound	Plant tissue	Elicitor	Increased of yield	Ref.
(1) Elicitation				
Phenolic acids	*Centella asiatica* L	Methyl jasmonate	122-Fold	81
Flavonoids			22.4-Fold	
Flavonols	*Vitis vinifera* L.	*Ascophyllum nodosum* extract	112%–308%	82
Anthocyanins	*Vitis vinifera* L. cv. Tinto Cão	Chitosan	47%–82.45%	83
Catechin			133.33%	
Flavonols			59.0%–105.8%	
Rosmarinic acid	*Melissa officinalis* L.	Heat stress	59%	84
Resveratrol	*Morus alba* L.	2-Hydroxypropyl-β-cyclodextrin	43-Fold	41
Oxyresveratrol			730-Fold	
Flavones	*Triticum aestivum* L.	Arachidonic acid	35%–58%	40
Luteolin 6-*C*-hexoside-*O*-hexoside			37%	
Luteolin 6-*C*-hexoside			44%	
Luteolin *O*-deoxyhexoside-*C*-hexoside			58%	
Apigenin *O*-hexoside-*O*-hexoside			41%	
Vanilic acid		Jasmonic acid	94%	
Syringic acid			47%	
Sinapic acid			77%	
Quercetin	*Allium cepa* L.	Methyl jasmonate	13.9-Fold	42

Phenolic compound	Substrate	Microorganism	Yield	Ref.
(2) Metabolic engineering				
Naringerin	Glucose/*p*-coumarate supplementation	*E. coli*	412 mg L^{-1}	85
Flavan-3-ols	Glucose	*E. coli*	40.7 mg L^{-1}	86
Kaempferol	Glucose	*S. cerevisiae*	26.57 mg L^{-1}	87
Quercetin	Glucose	*S. cerevisiae*	20.38 mg L^{-1}	87
Resveratrol	Glucose or ethanol	*S. cerevisiae*	415.65–531.41 mg L^{-1}	43
	Glicerol	*E. coli*	22.3 mg L^{-1}	44

5.1.2. Metabolic engineering (MBE). Metabolic engineering (MBE) of microorganisms is another interesting method to produce PC, with an advantage of not requiring complex extraction and purification methods like those used in the obtaining of these compounds from plant materials.[6] This biotechnology process is based on *de novo* synthesis, in which occurs the biotransformation of one substance into a new compound. The biosynthesis of PC in metabolic pathways in microorganisms, namely in *Escherichia coli* and *Saccharomyces cerevisiae*, has led to heterologous production of diverse PC. In Table 4 are presented results obtained with studies focused in polyphenol production by MBE of microorganisms.

MBE can be a viable economic alternative for the production of PC; however, in some cases the medium supplementation may be expensive/unable for industry, such as the use of *p*-coumarin acid as a precursor of target compounds. In this point, some studies have proposed the *de novo* biosynthesis from a cheap source of carbon. For instance, Li *et al.*[43] achieved high production of resveratrol by metabolic *S. cerevisiae* from glucose or ethanol (415.65 and 531.41 mg L^{-1}, respectively), through the tyrosine pathway. The use of coculture with two *E. coli* modified strains also made possible the formation of this bioactive stilbene from glycerol.[44] Naringenin, a central precursor of the majority of the flavonoids, also has been produced from xylose *via* a coculture system composed of *E. coli* and *S. cerevisiae.*[45]

5.2. Stability of phenolic compounds

To improve the PC stability, several techniques, such as the ones presented in Table 5, have been developed.

Encapsulation is one of the most used techniques to protect PC of the degradation. Diverse methods, such as spray drying (SD), freeze drying (FD), and complex coacervation, have been applied to obtain encapsulated PC.[46,47] SD and FD are the most applied techniques to encapsulate phytochemicals obtained from plant tissues; SD has the main advantages of being a fast process, with continuous production, and being simple and easy to increase, while FD is also a simple process, which requires low operating temperature and the absence of air, factors that result in less oxidative degradation and change in the structure of compounds;[48,49] however, these systems operate under extremely different conditions, and different encapsulation produces with distinct features.[46,48] For example, in the encapsulation of green tea extract using maltodextrin, β-cyclodextrin or their combination as wall materials, encapsulation by SD showed a smaller size and more regular format than FD. This behaviour was already expected, since the formation of microspheres by SD occurs instantly by pulverization of a solution in the hot surface. On the other hand, in the FD technique, the formation of ice is slow, which allows the formation of irregular structures. However, the efficiency of FD was higher than that of SD.[32] Similar results were found in the encapsulation of bioactive compounds obtained from *Hibiscus acetosella* Welw.[46] In these studies, this fact was explained due to the phenolic degradation by high temperature.[32,46] Increasing the drying temperature can also decrease the antioxidant capacity of bioactive compounds.[48] Furthermore, the thermal sensitivity of the target compound is crucial for the choice of the encapsulation method and wall material.[48,49]

The composition of the encapsulating agent also has impact on the physicochemical properties of the microencapsulated compounds, such as the particle size, porosity, water activity, dissolution rate, degradation rate, thermal resistance, and interaction with other substance, among others. Diverse materials have been used in the literature, since derivatives from hydrolysate starches are one of the most applied agents as wall materials due to their ability to improve aqueous solubility, low viscosity and being easy to dry.[50] High efficiency was achieved with pure MD in the microencapsulation of green tea and *P. granatum* polyphenols.[10,32] For anthocyanic compounds, this polysaccharide revealed promising results in the protection against thermal degradation and colour loss during storage.[11,51] Modified starches with octenyl succinic anhydride (OSA) combined with inulin, a fructooligosaccharide capable of improving viscoelastic properties and providing prebiotic activity of the particles, have been used to protect polyphenols during the baking process of cake without changing the product quality.[52] For PC, this blend of polymers with MD has improved mainly the stability to heating.[53,54] However, the behaviour of each class of PC can be different depending on the wall material composition. For instance, different blends of proteins with maltodextrin (soybean–maltodextrin (SP–MD) and whey protein–maltodextrin (WP–MD)) were tested to improve the stability of PC from grape juice, namely anthocyanins, flavanols, hydroxycinnamic acid derivatives and flavan-3-ols. As a result, the SP–MD system was the most efficient for anthocyanin stability. On the other hand, flavanols showed higher stability with the WM–MD system; however, both systems were unable to improve the stability of phenolic acids and flavan-3-ols.[54] Zein, a protein with high thermal resistance (until 200 °C), has been applied by electrospraying for encapsulation of polyphenols from *Euterpe oleracea* Mart. to protect them from thermal degradation during sterilization and baking processes.[55]

In particular, anthocyanin co-pigmentation has been shown to be an efficient way to achieve stability; molecular interaction of anthocyanins with other compounds leads to the accumulation of acyl in the pyran ring, which reduces the sensitivity of this flavonoids to the nucleophilic attack of water, consequently preventing anthocyanins from forming chalcones and losing their colour. Co-pigmentation of anthocyanins with phenolic acids, catechin and β-cyclodextrin has been proposed to increase the thermal stability and colour intensity of these compounds.[56,57]

In addition to increasing the stability and resistance to diverse factors of PC, encapsulation techniques can also mask some sensorial changes, such as taste modification and astringency, resulting from the addition of these compounds to a food matrix.[47,58] Also, an improvement of the bioavailability of these molecules has been achieved by these technologies.[55,59–63]Therefore, the complexity of each phytochemical, associated with the selected wall material and their

Table 5 Methods to improve the stability/bioavailability of phenolic compounds

Encapsulation technique	Carrier materials	Phenolic compounds	Source	Effects	Ref.
Complex coacervation	Gelatin/κ-carrageenan Gelatin-GA	Phenolic extract Phenolic extract	Cinnamon bark	Improving stability, resistance to processing and masking of astringency.	47
Atomization/coagulation	CA	Phenolic extract	*Rosmarinus officinalis* L.	Protection of bioactivities.	31
	NaAlg–$CaCl_2$	*p*-Hydroxybenzoic, *p*-coumaric, and protocatechuic acids	Commercial compounds	Protection of bioactivities.	7
Inclusion complex	β-CD	Catechin	Commercial compound	Increased solubility and resistance to heat, light and oxygen.	88
		Anthocyanins	*Rubus fruticosus* L.	Thermal resistance and stability after simulated gastrointestinal digestion.	89
	γ-CD	Taxifolin	Commercial compound	Increase in bioavailability (3.72-fold) in rats.	75
Spray drying	OSA-starch and insulin	Phenolic extract	*Bertholletia excelsa* H. B.K	High stability (120 days).	52
	MD	Phenolic extract	*Punica granatum* L.	Stability to storage (4 °C per 90 days), and protection of bioactivities.	10
	MD	Anthocyanins	*Euterpe edulis* M.; *Myrciaria cauliflora* Mart.	Protection of colour and bioactivities.	30 and 51
	MD–GA	Anthocyanins	Cherry juice	Colour stability at 38 °C per 60 days.	90
	MD–WP	Catechin	Grape juice	Improvement of thermal resistance	54
	MD–SP	Anthocyanins	Grape juice	improvement of thermal resistance; protection of colour and antioxidant activity (150 days).	54
	WP	Hydroxycitric acid	*Garcinia Cowa* Roxb.	Retained the antioxidant activity after the baking process.	53
	NaAlg–$CaCO_3$	Anthocyanins	*Grape skin*	Stability to light and heat; increased bioaccessibility.	61
	MD-PEC	Phenolic extract	*Crocus sativus* L. petals	High stability, protection of antioxidant activity, and improved bioaccessibility.	59
Freeze drying	MD/β-CD	Phenolic extract	*Camellia sinensis* L.	Retained the antioxidant activity.	32
	MD	Anthocyanins	*Myrciaria cauliflora* pomace	Thermal stability up to 150 °C; maintained stable colour up to 226 days.	11
	SP–GA	Anthocyanins	*Rubus idaeus* L.	High stability (37 °C per 60 days); improved bioaccessibility.	60
	GA	Phenolic extract	*Hibiscus acetosella*	Thermal stability.	46
Electrospraying	Zein	Phenolic extract	*Euterpe oleracea* Mart.	Thermal stability (up to 180 °C) and improved bioaccessibility.	55
Microemulsion	Labrasol	Anthocyanins	Commercial compounds and *Vaccinium angustifolium* Aiton	Improved bioaccessibility.	14
	Lecithin	Tangeretin	Commercial compound	Improved bioaccessibility.	71
Nanoliposomes	SL	Catechin and epigallocatechin gallate	Commercial compounds	Improvement of the stability and antioxidant activity.	62
	MD and chitosan	Anthocyanins	*Morus nigra* L.	Stability to heat and pH changes, improved bioavailability.	64
	Soybean phosphatidylcholine/ cholesterol	Phenolic extract	Coconut husk	Improved bioactivities; masked the brown dark colour.	58
	Tween 80, SL	Taxifolin	Commercial compound	Improved stability, antioxidant activity, and bioavailability.	63
	Lecithin	Phenolic extract	*Camellia sinensis* L.	Increased stability and preserved antioxidant activity.	91

Table 5 *(Contd.)*

Encapsulation technique	Carrier materials	Phenolic compounds	Source	Effects	Ref.
Solid lipid nanoparticles	SL	Puerarin	Commercial compound	Improved the bioavailability (3-fold) in rats.	66
	Phospholipon® 90G	Resveratrol	Commercial compound	Increased oral bioavailability (8.035-fold) in rats.	67
Superparamagnetic iron oxide nanoparticles		Quercetin	Commercial compound	Increased bioavailability.	21
Other methods specific to anthocyanins					
Co-pigmentation with β-CD			*Phaseolus vulgaris* L.	Increased stability and protected the colour.	56
Co-pigmentation with catechin or ferulic acid.			Commercial compound	Improvement of the thermal stability and of the colour.	57
Bleaching treatment			*Vaccinium corymbosum* L.	Increased bioaccessibility.	68

MD – Maltodextrin; GA – gum arabic; SPI – soybean protein; WP – whey protein; CA – calcium alginate; MMS – modified maize starch; CD – cyclodextrin; SL – soy lectin; PEC – pectin; MPS – modified potato starch; NaAlg – sodium alginate; $CaCO_3$ –calcium carbonate; $CaCl_2$ – calcium chloride.

interaction with other compounds, makes the choice of the encapsulation technique more appropriate in a thorough and individual study.

5.3. Bioavailability of phenolic compounds

PC are recognized and treated by the body in the same way as xenobiotics, being metabolized so that they are rapidly excreted. These compounds must be absorbed and distributed through the body's bloodstream and/or lymphatic systems;[4] the amount of compounds available to undergoe this process is known as bioavailability. In general, PC have low bioavailability, so it is estimated that the rate of absorption of CP ranges from 0.3 to 43%.[1,4] Furthermore, when a PC is ingested, another factor, denoted as bioaccessibility, which corresponds to the fraction of a compound that is released from the food matrix to the gastrointestinal tract and becomes available for the absorption process, must also be considered.[4] Therefore, several aspects can influence bioaccessibilitiy of these compounds, such as the chemical structure, water solubility, food processing, interaction with other compounds, and dietary intake, among others.[4] Besides the mentioned factors, the bioavailability is also influenced by the digestion and metabolization process, where these compounds are subjected to various chemical changes, namely biotransformation.[4,12] These processes can change the PC structures, which interfere in the reactions and may interfere with the next stages of the absorption process. Complex PC, such as hydrolysable and condensed tannins, must be hydrolysed into smaller molecules (tri, di and monomers) to be absorbed; enzymatic reactions that occur at the level of small intestine are not able to break these molecules, being then taken to the large intestine, where only bacterial fermentation reduces these PC; only after this process, the hydrolysed compounds are transported to the liver or are excreted.[4,12]

Facing the complexity of PC absorption, different techniques are being developed to minimize the PC interactions described above, improving chemical protection and targeted delivery (Table 5). Nanoencapsulation techniques using appropriate wall materials have showed potential to protect the polyphenols of the metabolic reactions; besides that they allow the selection of the desired effect or specific tissue on which these compounds should exert their actions.[4] For example, the change of pH values is a factor that interferes in the anthocyanin's stability, which can lead to their degradation under gastrointestinal conditions (pH 2–6.8). To improve the resistance of these compounds during digestion and their bioavailability, encapsulation by emulsification with NaAlg and $CaCO_3$ by freeze or spray drying showed a retention efficiency of 70% and 83% after *in vitro* gastric digestion, and 24.5% and 15% in the end of intestinal digestion, respectively.[61] The use of nanoliposomes is another technique that can be used to improve the stability of PC in alkaline pH.[4] By this method, it was possible to keep the encapsulated anthocyanins stable up to pH 7.5.[64] Electrospray encapsulation with zein protein also has showed protection against low pH to PC from *E. oleracea.*[55] Lipid-based nanocarriers, *e.g.* nano-emulsions, nano-liposomes, solid lipids and nanoparticles, have shown promise to increase the bioaccessibility of phenolic compounds in the body due to their capacity to improve solubility, stability on gastric condition and release of these compounds in a controlled way.[65] For example, solid-lipid nanoparticles have been used to improve absorption of PC that have poor water-solubility.[65–67] In addition, this technique associated with purified phosphatidylcholine (Phospholipon® 90G) as the encapsulation material was able to preserve the integrity of resveratrol at low stomach pH.[67]

Interesting, besides technological techniques, simple methods can also be used to increase the bioavailability of PC. For instance, anthocyanins' absorption from highbush blueberry (*Vaccinium corymbosum* L.) purée in the human body has been improved after bleaching as pre-treatment.[68]

6. Concluding remarks and future perspectives

Several studies have presented PC as a natural alternative for the treatment and prevention of several diseases, such as

cancer, cardiovascular disorders and neurodegeneration; in addition, these compounds can be used in the formulation of cosmetics that act on pathologies or conditions harmful to the skin, which increase the interest in the use of these bioactive molecules in pharmaceutical products. PC are an alternative to artificial food additives and can be interesting for the development of functional foods that aim to maintain good health. However, there are still some gaps that need to be better studied so that the use of these compounds can reach a large industrial scale and for their administration and consumption to be effective and efficient to guarantee their benefits without causing a side effect. Still for application in the food industry, methods to increase the stability and to preserve the bioactivity of these compounds during the useful life of food products must be investigated.

As presented in this review, more effective methods for the viable use of these compounds have been developed, which makes us believe that the practical application of these natural molecules tends to become more frequent in different industries, such as pharmaceutical, food, cosmetics, textile and others.

Conflicts of interest

The authors declare no conflict of interest.

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