Review

Employ of Anthocyanins in nanocarriers for Nano Delivery: *In Vitro* and *In Vivo* Experimental Approaches for Chronic Diseases

Ana C. Gonçalves[1,2], Amílcar Falcão[2,3], Gilberto Alves[1], João A. Lopes[4] and Luís R. Silva[1,5*]

[1]   CICS-UBI—Health Sciences Research Centre, University of Beira Interior, 6201-001 Covilhã, Portugal; ana-carolinagoncalves@sapo.pt (A.C.G.); gilberto@fcsaude.ubi.pt (G.A.)

[2]   CIBIT—Coimbra Institute for Biomedical Imaging and Translational Research, University of Coimbra, 3000-548 Coimbra, Portugal

[3]   Laboratory of Pharmacology, Faculty of Pharmacy, University of Coimbra, 3000-548 Coimbra, Portugal; acfalcao@ff.uc.pt

[4]   iMed.ULisboa, Research Institute for Medicines, Faculdade de Farmácia, University of Lisboa, 1649-003 Lisboa, Portugal; jlopes@ff.ulisboa.pt

[5]   CPIRN-UDI/IPG, Center of Potential and Innovation of Natural Resources, Research Unit for Inland Development (UDI), Polytechnic Institute of Guarda, 6300-559 Guarda, Portugal

[*]   Correspondence: luisfarmacognosia@gmail.com; Tel.: +351-275-329-077

Abstract: Anthocyanins are among the best-known phenolic compounds and possess remarkable biological activities, including antioxidant, anti-inflammatory, anticancer, and antidiabetic effects. Despite their therapeutic benefits, they are not widely used as health-promoting agents due to their instability, low absorption, and thus, low bioavailability and rapid metabolism in the human body. Recent research suggests that the application of nanotechnology could increase their solubility and/or bioavailability, and thus, their biological potential. Therefore, in this review, we decided to provide, for the first time, a comprehensive overview of *in vitro* and *in vivo* studies on nanocarriers used as delivery systems of anthocyanins, and their aglycones, i.e., anthocyanidins alone or combined with conventional drugs to the treatment or management of chronic diseases.

Keywords: bioactive compounds; anthocyanins; drug delivery system; nanoparticles; chronic diseases; health benefits

1. Introduction

Considering the increasing prevalence of chronic diseases worldwide and the emerging need to find safer, more effective, cheaper, and low toxic new therapeutic agents, it is not surprising that phenolic compounds are receiving special attention and importance [1,2]. These secondary metabolites are produced by plants to promote their normal cell metabolism and protect them from abiotic (e.g., humidity, light, temperature, moisture, soil, water, pH and salinity) and biotic factors (e.g., microbial infections) [3]. Their daily consumption by individuals is also promoted and considered a useful strategy to promote health status and prevent numerous diseases, with fewer or no side effects, unlike conventional drugs [3–5]. In fact, phenolics have been used in traditional medicines since ancient times due to their remarkable ability to relieve gastrointestinal complaints, pain, headaches, colds, coughs, and others [6,7]. Therefore, old proverbs, such as "an apple a day keeps the doctor away", are more relevant than ever.

Among these natural molecules, special attention has been paid to anthocyanidins, and their glycosides, i.e., anthocyanins [8]. Both of them are water-soluble and non-toxic natural compounds, which have high molecular weight and are very affordable. They are considered to be the main contributors to blue-violet and red colours of many fruits, flowers and vegetables [9]. In addition, there is a great demand and many potential applications, because they show remarkable effects as antioxidant, anti-inflammatory,

antimutagenic, antidiabetic, and anticancer agents both *in vitro* and *in vivo*, provide neurological and cardiovascular protection, improve memory (Figure 1), and can be used as additives for beverages, foods, and cosmetics [8,10,19,11–18]. However, anthocyanidins and anthocyanins have low bioavailability because they are poorly absorbed, rapidly metabolized and excreted, which, in turn, compromises their biological and pharmacological benefits [13]. Besides, their high susceptibility to environmental factors, such as chemical factors (e.g., ascorbic acid, light, metal ions, oxygen, pH), processing (e.g., heat), and gastrointestinal digestive processes (enzymes, proteins, and pH) make them highly sensitive, reactive, unstable, and susceptible to decomposition [9,20]. Additionally, both have the ability to irreversibly bind with some molecules, resulting in structural changes, and consequently, making them inaccessible for absorption [13].
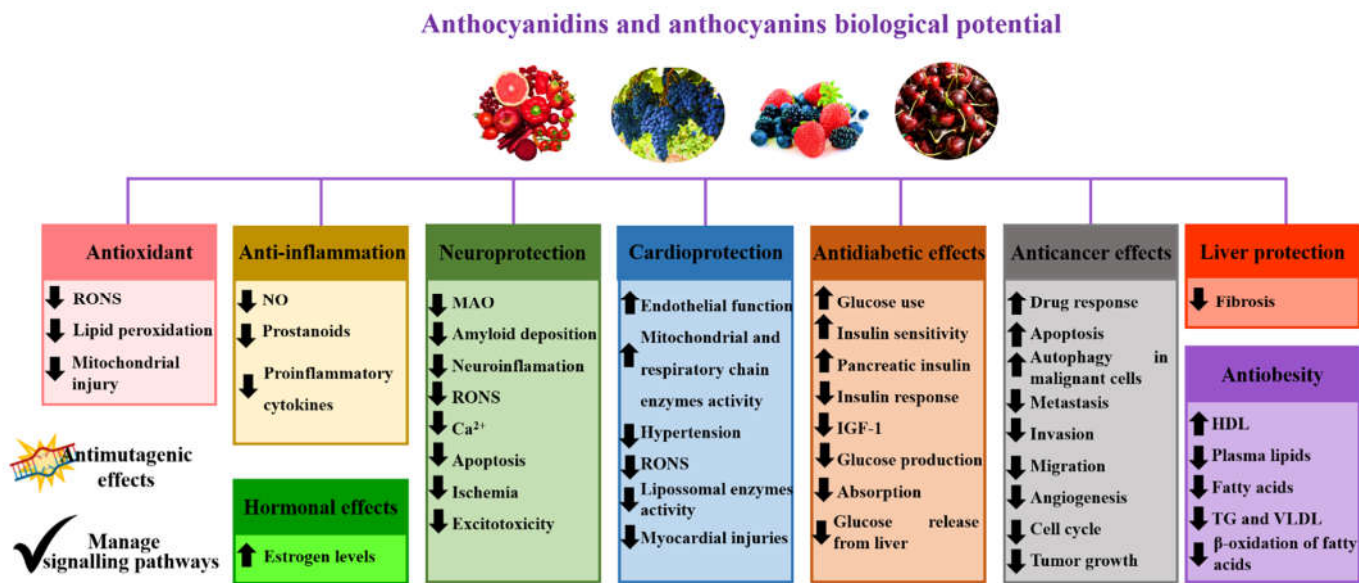

Figure 1. Main biological potential attributed to anthocyanidins and anthocyanins. ↑: increase; ↓: decrease; RONS: reactive oxygen and nitrogen species; NO: nitric oxide; MAO: Monoamine oxidase; IGF-1: Insulin-like growth factor 1; TG: triglycerides; VLDL: very low-density lipoprotein; HDL: high-density lipoprotein. Adapted from [8,10,19,11–18].

In view of the above, and in order to overcome these drawbacks and improve their pharmacokinetic, pharmacodynamic and therapeutic properties, i.e. their bioaccessibility, bioactivity, absorption, stability in the gastrointestinal tract, solubility and/or better control of their release, the development of novel delivery systems may be an important approach, mainly thanks to their ability to form a physical barrier between anthocyanins and destabilizing factors, protecting them from degradation and enhancing their biological potential [21–26]. Several methods exist for improvement of drug delivery, namely physical (electrospinning/electrospraying, freeze- and spray-drying, lyophilization), chemical (complexation processes) and/or a combination of both (liposomal systems, emulsification, gelation, coacervation) [13,20]. The main biopolymers used for encapsulation are polysaccharides, such as cellulose, chitosan, mucilages, natural gums, pectin, starch, and derivatives, and proteins, such as caseinate, gelatine, soy protein and whey [9,27–29]. Moreover, the encapsulation of anthocyanins also allows for their use at the industrial level [30]. Therefore, taking into account all these aspects, the main objective of this work was to provide a comprehensive review of *in vitro* and *in vivo* studies on nanocarriers employed to deliver anthocyanins and anthocyanidins alone or in combination with active pharmaceutical ingredients.

2. Study selection

A detailed and comprehensive search was conducted in August 2022 on Google Scholar, Medline (PubMed), National Center for Biotechnology Information (NCBI), ResearchGate, Science Direct, Scopus, SpringerLink and Web of Science databases to found publications on the therapeutic *in vitro* and *in vivo* effects of encapsulated anthocyanins and anthocyanidins. The following free terms, keywords, or MeSH terms were used: anthocyanins, anthocyanidins, in vivo, antioxidant potential, anti-inflammatory, chronic disease, encapsulation, drug delivery systems, health-promoting properties, health benefits, nanoparticles, nanocapsules, nanostructures, nanoparticle technology, bioactive compounds, bioactivity, bioavailability and absorption, combined with the operator AND, OR, or NOT. There were no restrictions on the literature search in terms of author(s) or type of publication. All selected articles were written in English. The final database included 211 references, and most of the selected articles used in this review were from 2016-2022.

3. Anthocyanins: upcoming remarkable active molecules

Anthocyanidins and their glycosides (i.e., anthocyanins) are natural pigments synthesized through the general flavonoid pathway and their main role is to protect plants from stress factors and promote normal cellular metabolism [3,31]. To date, about 30 different aglycones have been described [32]. Among them, cyanidin, delphinidin, malvidin, pelargonidin, peonidin and petunidin are the most abundant (Table 1 and Figure 2) [33]. Like other flavonoid compounds, anthocyanidins and anthocyanins have a carbon skeleton of C6 (A ring)-C3 (C ring)-C6 (B ring) being the C-ring a heterocyclic ring with an oxygen atom (Figure 2) [31]. Once unstable aglycones are found in nature mainly in conjugation with sugar residues, usually found at carbon 3 [31]; additional sugars are usually attached to carbons 5 and/or 7 or, less commonly to carbons 3' and 5' [34,35]. In general, the predominant sugars are arabinose, galactose, glucose, rhamnose, rutinose, and xylose, among others [36] (Figure 2). These sugar residues can also be acylated with aliphatic acids (e.g., acetic malonic, malic and oxalic acids) and/or aromatic acids (e.g., caffeic, ρ-coumaric, ferulic, sinapic and ρ-hydroxybenzoic acids) [31]. Therefore, it is not surprising that the number and type of sugar units attached to the aglycone, as well as the number, position, and degree of methylation of the hydroxyl groups, and the position of aromatic and/or carboxylated aliphatic acids on the sugar residue affect their biological potential [36–39]. In general, hydroxylation and methoxylation are considered to be the major contributors to the colour and stability of anthocyanins [36–38]. Basically, as the number of hydroxyl groups increases, they tend to turn blue, but their stability is lower [40]. On the other hand, methoxylation on the B ring mediated by *O*-methyltransferases increases their stability and favours the appearance of red colours [38]. For example, due to its numerous hydroxyl groups, delphinidin shows higher antioxidant activity than petunidin, which, in turn, has the lowest antioxidant activity among the six most abundant anthocyanins [36].
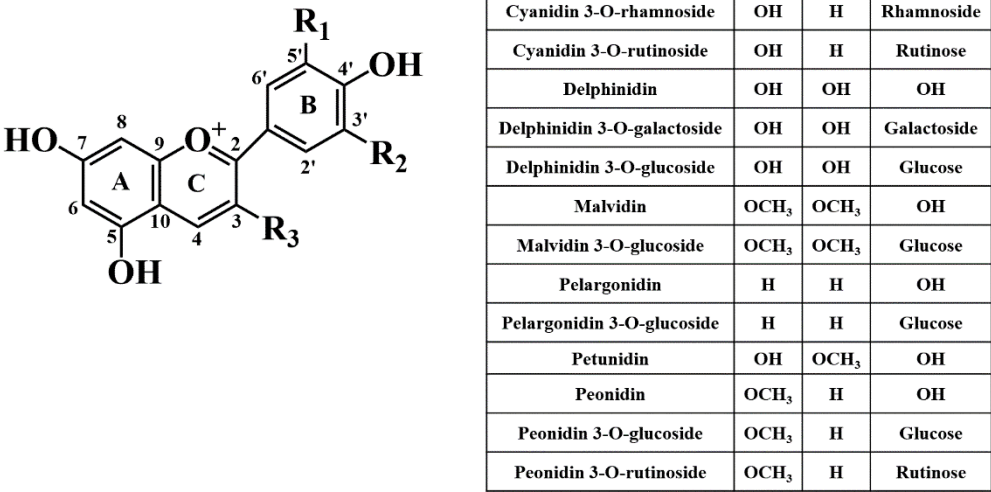
	R_1	R_2	R_3
Cyanidin	OH	H	OH
Cyanidin 3-O-arabinoside	OH	H	Arabinoside
Cyanidin 3-O-galactoside	OH	H	Galactoside
Cyanidin 3-O-glucoside	OH	H	Glucose
Cyanidin 3-O-rhamnoside	OH	H	Rhamnoside
Cyanidin 3-O-rutinoside	OH	H	Rutinose
Delphinidin	OH	OH	OH
Delphinidin 3-O-galactoside	OH	OH	Galactoside
Delphinidin 3-O-glucoside	OH	OH	Glucose
Malvidin	OCH$_3$	OCH$_3$	OH
Malvidin 3-O-glucoside	OCH$_3$	OCH$_3$	Glucose
Pelargonidin	H	H	OH
Pelargonidin 3-O-glucoside	H	H	Glucose
Petunidin	OH	OCH$_3$	OH
Peonidin	OCH$_3$	H	OH
Peonidin 3-O-glucoside	OCH$_3$	H	Glucose
Peonidin 3-O-rutinoside	OCH$_3$	H	Rutinose

Figure 2. Basic chemical structure of the main anthocyanidins and their glycosides anthocyanins found in nature.

Moreover, different pH conditions lead to different colours and affect the stability of anthocyanins [41]. As far as we know, anthocyanins are more stable under acidic conditions [31]. Moreover, pH values below 3 contribute to the formation of red and orange anthocyanin compounds, as flavylium cations predominate here, and increase their water solubility, while pH values of 6 to 7 favour the appearance of violet species, and pH values above 7 to 8 lead to the appearance of the blue colour (Figure 3) [42–44]. In contrast, at basic pH, anthocyanins are oxidised and degraded, losing their colour as they kinetically and thermodynamically compete for the hydration of flavylium ions, leading to the formation of carbinol pseudobases, chalcones and quinonoid anions [31,45]. The chemical degradation of chalcones leads to the formation of phenolic acids [9,46].
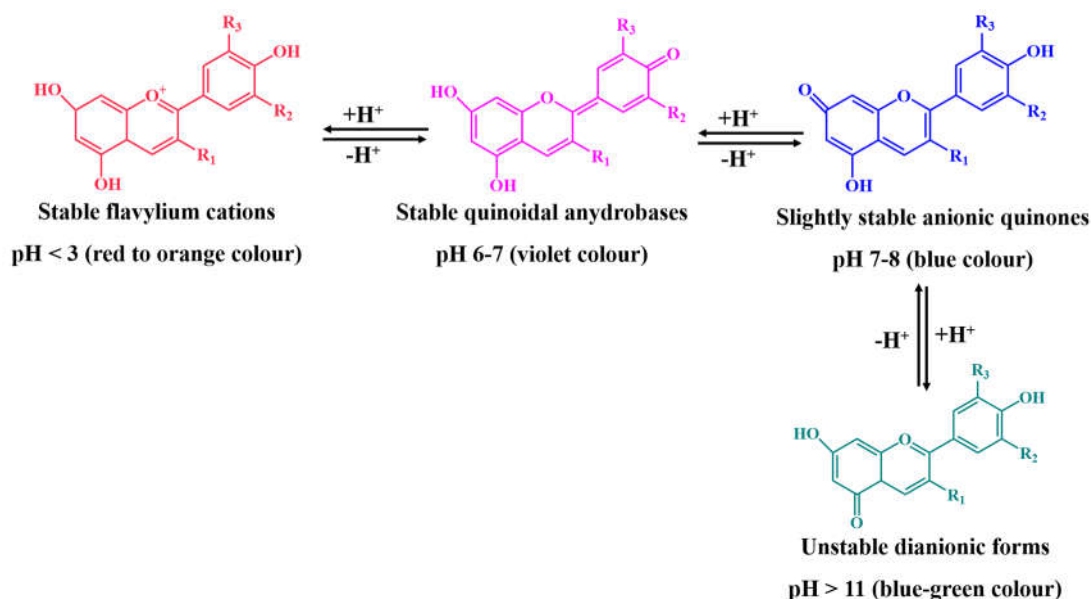
Figure 3. Structural forms and colours shown by anthocyanins at different pH values (R_1=H or sugar moiety; R_2 and R_3= hydrogen atom or methyl group).

Other factors that increase the sensitivity of anthocyanins include storage and processing conditions, temperature, concentration, and exposure to light, oxygen, other phenolic compounds, proteins (such as enzymes), molecules (such as water), sulfites and metal ions [21,40,47–49].

3.1. Anthocyanins rich-sources

Anthocyanins and their aglycones are the main contributors to the colour of many fruits, flowers and vegetables and are considered the key of the biological potential associated to these products [39]. The recommended daily intake is over 100 mg and range up to 1000 mg per day. However, Zamora-Ros and co-workers [50] reported that the total intake of anthocyanins in Europe ranges from 19.3 to 64.88 mg per day in men, and from 18.73 to 44.08 mg per day in women. In contrast, in the United States of America (USA), daily consumption ranges from 180–215 mg [51]. Among anthocyanin-rich sources, in Europe, apples, berries, grapes, and pears (50%), and red wine (21%) are the main contributors to daily anthocyanin intake, while in the USA, berries, wine, grapes, and bananas (20, 16, 11 and 11%, respectively) are the main ones [52].

Indeed, anthocyanins possess remarkable and recognised health-promoting properties, so, it is highly recommended to increase their consumption to promote health status and prevent the occurrence and/or development of chronic diseases [19,29,53]. Thus, strong correlations have already been reported between the total amount of anthocyanins extracted from sweet cherries and the ability to inhibit the enzyme α-glucosidase (r = 0.9929) and to affect the growth of colon adenocarcinoma Caco-2 cells (r = 0.6674) [11]. In addition, recent studies have shown that anthocyanins have remarkable abilities to reduce oxidative stress in hepatocellular HepG2 carcinoma cells [10], as well as impair the growth of AGS gastric cancer cells and reduce inflammatory iNOs and COX-2 expression and resulting nitric oxide radicals on RAW 264.7 macrophages [12].

Anthocyanidins and anthocyanins are widely distributed in nature [39]. The most important of them are listed in Table 1. Cyanidin derivatives are the most abundant in plants, especially cyanidin 3-*O*-glucoside and 3-*O*-rutinoside, followed by delphinidin and pelargonidin glycosides, and finally peonidin, malvidin, and petunidin methylated derivatives [54]. As for fruits, açaí is probably one of the most anthocyanin-rich fruits, with a total anthocyanin content (TAC) varying between 1020.00-1433.00 mg of cyanidin 3-*O*-glucoside (C3G) per 100 g fresh weight (fw), with a predominance of cyanidin 3-*O*-rutinoside and cyanidin 3-*O*-glucoside [55,56]. Red berries also have considerable

amounts of anthocyanins and are capable of providing substantial amounts of anthocyanins doses in a single serving, contrasting with blueberries, whose TAC values range from 34.50 to 552.20 and from 69.97 to 378.31 mg C3G per 100 g of fw for highbush and rabbit-eye blueberries, respectively [57–62]. Regarding the profile of anthocyanins in highbush blueberries, they have higher amounts of malvidin 3-*O*-galactoside, peonidin 3-*O*-glucoside, delphinidin 3-*O*-glucoside and delphinidin 3-*O*-galactoside, while rabbit-eye blueberries are richer in peonidin 3-*O*-glucoside, malvidin 3-*O*-glucoside, malvidin 3-*O*-arabinoside, and delphinidin 3-*O*-galactoside [57,63]. Elderberries and chokeberry also have considerable amounts of anthocyanins (130.80-953.00 and 428.00 mg C3G per 100 g of fw, respectively), as do blueberries (280.98-329.00 mg C3G per 100 g of fw), haskap (88.30-273.00 mg C3G per 100 g of fw), black currants (62.80-271.33 mg C3G per 100 g of fw), red grapes (0.30-164.20 mg C3G per 100 g of fw) and red raspberries (21.90-62.50 mg C3G per 100 g of fw) [64–70]. In addition, sour and sweet cherries also have significant amounts of anthocyanins, with TAC values ranging from 10.50-87.40 mg C3G per 100 g of fw for tart cherries and 1.03-179.14 mg C3R per 100 g of dw for sweet cherries [71–73]. Comparing the anthocyanin profile of both cultivars, sweet cherries have higher levels of cyanidin 3-*O*-rutinoside and cyanidin 3-*O*-glucose, while cyanidin 3-*O*-glucosyl-rutinoside is the predominant anthocyanin in sour cherries [72,74–77].

In vegetables, TAC levels around 150 mg C3G per 100 g fw are found in eggplant, purple sweet potato, and red cabbage. Among anthocyanins, delphinidin 3-*O*-rutinoside is the predominant one in eggplant [78], while 3-*O*-sophoroside-5-glucoside derivatives of peonidin and cyanidin are the most important in purple sweet potato [79]. On the other hand, cyanidin-3-diglucoside-5-glucoside, cyanidin-3-(sinapoyl)(sinapoyl)-diglucoside-5-glucoside and cyanidin-3-(ρ-coumaroyl)-diglucoside-5-glucoside are most commonly in red cabbage [80].

Compare to beverages, elderberry juices are richest in anthocyanins, with values ranging from 90.00 to 5270.00 mg C3G per litre [81]. Among anthocyanins, cyanidin-3-*O*-sambubioside predominates, followed by cyanidin-3-*O*-glucoside and cyanidin-3-*O*-sambubioside-5-*O*-glucoside [82]. In addition, blueberry juices also contain considerable amounts of anthocyanins, with values varying from 317.07 to 588.87 mg C3G per litre [83]. In contrast to elderberry juices, malvidin 3-*O*-glucoside and malvidin 3-*O*-galactoside are most abundant in blueberry juices [84]. Raspberry juices are also rich in anthocyanins, and have TAC values around 336.70 mg C3G per litre [85]. In addition, pomegranate juices and red wines exhibit similar amounts of anthocyanins (with average values around 200 mg C3G per litre) [85–88].

Of course, it should be noted that anthocyanin content is highly dependent on genotype/variety, climate, ripening stage, local origin, agronomic and postharvest practices and conditions [89]. For example, Howard et al. [90] reported that blueberry jams stored at 4 °C had 65% more anthocyanins after 6 months of storage than those stored at 25 °C. Similar data were obtained for their juices after an 8-month study [84].

Table 1. Main anthocyanins-rich natural sources.

Main sources	Scientific name	Total anthocyanins content (mg C3G/100 g fw)	Main anthocyanins found	References
Fruits				
Açaí	*Euterpe oleracea*	1020.00-1433.00	Cyanidin 3-(acetyl)hexose Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Cyanidin 3,5-hexose pentose Pelargonidin 3-*O*-glucoside Peonidin 3-*O*-glucoside Peonidin 3-*O*-rutinoside	[55,56]
Acerola	*Malphigia emarginata*	23.00-48.00	Cyanidin 3-*O*-rhamnoside Pelargonidin 3-*O*-rhamnoside Cyanidin Pelargonidin	[56,91]
Apple	*Malus domestica*	<0.01-8.22	Cyanidin 3-*O*-diglucoside-5-*O*-glucoside Cyanidin 3-*O*-(6″-ρ-coumaroyl-glucoside) Peonidin 3-*O*-sambubioside-5-*O*-glucoside Cyanidin 3,5-*O*-diglucoside Delphinidin 3-*O*-xyloside Delphinidin 3-*O*-glucosyl-glucoside Cyanidin 3-*O*-(2-*O*-(6-*O*-(E)-caffeoyl-D glucoside)-D-glucoside)-5-*O*-D-glucoside Delphinidin 3-*O*-galactoside	[92,93]
Bilberry	*Vaccinium myrtillus*	280.98-329.00	Cyanidin 3-*O*-arabinoside Cyanidin 3-*O*-galactoside Cyanidin 3-*O*-glucoside Delphinidin 3-*O*-arabinoside Delphinidin 3-*O*-galactoside Delphinidin 3-*O*-glucoside Malvidin 3-*O*-arabinoside Malvidin 3-*O*-galactoside Malvidin 3-*O*-glucoside Petunidin 3-*O*-arabinoside Petunidin 3-*O*-galactoside Petunidin 3-*O*-glucoside Peonidin 3-*O*-galactoside Peonidin 3-*O*-glucoside	[67,94,95]
Blackberry	*Rubus fruticosus*	12.30-150.00	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Cyanidin 3-*O*-xyloside Cyanidin 3-*O*-malonyl-glucoside Cyanidin 3-dioxalylglucoside	[96,97]
Black currant	*Ribes rubrum*	62.80-271.33	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Delphinidin 3-*O*-glucoside Delphinidin 3-*O*-rutinoside	[92,98]
Rabbiteye blueberry	*Vaccinium ashei*	69.97-378.31	Cyanidin 3-*O*-arabinoside Cyanidin 3-*O*-galactoside Cyanidin 3-*O*-glucoside Delphinidin 3-*O*-arabinoside Delphinidin 3-*O*-galactoside Delphinidin 3-*O*-glucoside Malvidin 3-*O*-arabinoside Peonidin 3-*O*-glucoside Peonidin 3-*O*-arabinoside	[57–60]

			Peonidin 3-*O*-galactoside	
			Petunidin 3-*O*-galactoside	
			Petunidin 3-*O*-glucoside	
			Petunidin 3-*O*-arabinoside	
Highbush blueberry	*Vaccinium corymbosum*	34.50-552.20	Cyanidin 3-*O*-arabinoside Cyanidin 3-*O*-galactoside Cyanidin 3-*O*-glucoside Delphinidin 3-*O*-galactoside Delphinidin 3-*O*-glucoside Delphinidin 3-*O*-arabinoside Malvidin 3-*O*-arabinoside Malvidin 3-*O*-galactoside Malvidin 3-*O*-glucoside Petunidin 3-*O*-galactoside Petunidin 3-*O*-glucoside Peonidin 3-*O*-arabinoside Peonidin 3-*O*-galactoside Petunidin 3-*O*-arabinoside	[58,60–62]
Cranberry	*Vaccinium macrocarpon*	11.10-32.00	Cyanidin 3-*O*-galactoside Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-xyloside	[65,99]
Chokeberry	*Aronia melanocarpa*	428.00	Cyanidin 3-*O*-arabinoside Cyanidin 3-*O*-galactoside Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-xyloside	[65]
Elderberry	*Sambucus nigra*	130.80-953.00	Cyanidin 3,5-diglucoside Cyanidin 3-sambubioside-5-glucoside Cyanidin-3-*O*-glucoside Cyanidin 3-*O*-sambubioside	[64,67,100,101]
Fig	*Ficus carica*	2.57-9.70	Cyanidin 3,5-diglucoside Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside	[102,103]
Lingonberry	*Vaccinium vitis-idaea*	45.00	Cyanidin 3-*O*-arabinoside Cyanidin 3-*O*-galactoside Cyanidin 3-*O*-glucoside Peonidin3-*O*-glucoside	[65]
Haskap	*Lonicera caerulea*	88.30-273.00	Cyanidin 3,5-diglucoside Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Pelargonidin 3-*O*-glucoside Peonidin 3-*O*-glucoside Peonidin 3,5-diglucosid	[104–106]
Nectarine	*Prunus persica* var.*nucipersica*	0.21-0.59	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside	[107,108]
Peach	*Prunus persica*	0.15-0.44	Cyanidin-3-*O*-glucoside, Cyanidin-3-*O*-rutinoside	[109,110]
Plum	*Prunus domestica*	13.70-33.11	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Cyanidin 3-*O*-xyloside Peonidin 3-*O*-glucoside Peonidin 3-*O*-rutinoside	[92,111]
Pomegranate	*Punica granatum*	17.95-36.41 [1]	Cyanidin-3,5- diglucoside Cyanidin 3-*O*-glucoside Delphinidin 3-*O*-glucoside Delphinidin-3,5- diglucoside Pelargonidin 3-*O*-glucoside Pelargonidin-3,5- diglucoside	[112–114]

Red currant	*Ribes rubrum*	7.10-19.30	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Delphinidin Delphinidin 3-*O*-glucoside Delphinidin 3-*O*-rutinoside	[115,116]
Red grape	*Vitis vinifera*	0.30-164.20	Delphinidin 3-*O*-glucoside Cyanidin 3-*O*-glucoside Petunidin 3-*O*-glucoside Peonidin 3-*O*-glucoside Malvidin 3-*O*-glucoside Cyanidin 3-(acetyl)hexose Petunidin 3-(acetyl)glucoside Peonidin 3-(acetyl)glucoside Malvidin 3-(acetyl)glucoside Peonidin 3-ρ-coumaroyl glucoside Malvidin 3-ρ-coumaroyl glucoside	[66,117–119]
Red pear	*Pyrus communis*	1.20-12.0 [1]	Cyanidin 3-*O*-galactoside Cyanidin 3-*O*-glucoside Cyanidin pentoside Cyanidin 3-*O*-arabinoside Cyanidin 3-*O*-rutinoside Peonidin 3-*O*-galactoside Peonidin 3-*O*-galactoside	[120,121]
Red raspberry	*Rubus idaeus*	21.90-62.50	Cyanidin 3-*O*-sophoroside Cyanidin 3-(2-glucosylrutinoside) Cyanidin 3-*O*-glucoside Cyanidin 3-(2-glucosylrutinoside) Cyanidin 3-*O*-xylosylrutinoside Pelargonidin 3-*O*-sophoroside Cyanidin 3-*O*-rutinoside Pelargonidin 3-(2-glucosylrutinoside) Pelargonidin 3-*O*-glucoside Pelargonidin 3-*O*-rutinoside	[69,70]
Strawberry	*Fragaria × ananassa*	29.00-49.43	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Cyanidin 3-malonylglucose-5-glucose Delphinidin 3-*O*-glucoside Malvidin 3-*O*-glucoside Pelargonidin 3-*O*-glucoside Pelargonidin 3-*O*-rutinoside Pelargonidin 3-(acetyl)glucoside	[67,92,122,123]
Sweet cherry	*Prunus avium*	1.03-179.14 *	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Delphinidin 3-*O*-rutinoside Peonidin 3-*O*-rutinoside	[71,74,75]
Tamarillo	*Solanum betaceum*	29.70-481.37 [2]	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Delphinidin 3-*O*-rutinoside Pelargonidin 3-*O*-rutinoside	[124]
Sour cherry	*Prunus cerasus*	10.50-87.40	Cyanidin 3-*O*-glucorutinoside Cyanidin-3-O-glucoside Cyanidin-3-O-rutinoside	[73,125]
Tomato	*Solanum lycopersicum*	4.35-7.09 [1]	Delphinidin 3-(cis-ρ-coumaroyl)-rutinoside-5-glucoside Petunidin 3-(caffeoyl)-rutinoside-5-glucoside Delphinidin 3-(*trans*-ρ-coumaroyl)-rutinoside-5-glucoside	[126,127]

			Delphinidin 3-(feruloyl)-rutinoside-5-glucoside	
			Petunidin 3-(*cis-p*-coumaroyl)-rutinoside-5-glucoside	
			Petunidin 3-(*trans-ρ*-coumaroyl)-rutinoside-5-glucoside	
			Petunidin 3-(feruloyl)-rutinoside-5-glucoside	
			Malvidin 3-(*cis-ρ*-coumaroyl)-rutinoside-5-glucoside	
			Malvidin 3-(*trans-ρ*-coumaroyl)-rutinoside-5-glucoside	
			Malvidin 3-(feruloyl)-rutinoside-5-glucoside	
			Petunidin 3-(*trans- ρ*-coumaroyl-rhamonside)-glucoside-5-glucoside	
			Malvidin 3-(*ρ*-methoxy-*trans*-coumaroyl)-rutinoside-5-glucoside	
		Vegetables		
Black carrot	*Daucus carota* ssp. *sativus* var. *atrorubens*	1.50-17.70	Cyanidin 3-xylosyl(glucosyl)galactoside Cyanidin 3-xylosylgalactoside Cyanidin 3-xylosyl(*ρ*-hydroxybenzoylglucosyl)galactoside Cyanidin 3-xylosyl(sinapoylglucosyl)galactoside Cyanidin 3-xylosyl(feruloylglucosyl)galactoside Cyanidin 3-xylosyl(coumaroylglucosyl)galactoside Pelargonidin 3-xylosyl(feruloylglucosyl)galactoside Peonidin 3-xylosylgalactoside Peonidin 3-xylosyl(sinapoylglucosyl)galactoside Peonidin 3-xylosyl(feruloylglucosyl)galactoside	[128]
Eggplant	*Solanum melongena*	14.86-182.44	Delphinidin 3-rutinoside-5-glucoside Delphinidin 3-rutinoside-glucoside Delphinidin 3-*O*-glucoside Delphinidin 3-*O*-rutinoside	[78,129]
Purple sweet potato	*Dioscorea alata*	4.91-150.00	Cyanidin 3-sophoroside-5-glucoside Peonidin 3-sophoroside-5-glucoside Cyanidin 3-*ρ*-hydroxybenzoylsophoroside-5-glucoside Peonidin 3-*ρ*-hydroxybenzoylsophoroside-5-glucoside Delphinidin 3,5-diglucoside Cyanidin 3-(6''-feruloylsophoroside)-5-glucoside Peonidin 3-(6''-feruloylsophoroside)-5-glucoside Cyanidin 3-(6''-caffeoylsophoroside)-5-glucoside Cyanidin 3-caffeoyl-*ρ*-hydroxybenzoyl sophoroside-5-glucoside Cyanidin 3-(6''-caffeoyl-6'''-feruloylsophoroside)-5-glucoside Peonidin 3-caffeoyl sophoroside-5-glucoside Peonidin-3-caffeoyl-*ρ*-hydroxybenzoyl sophoroside-5-glucoside Peonidin-3-(6''-caffeoyl-6'''-feruloylsophoroside)-5-glucoside	[79,130,131]
Red cabbage	*Brassica oleracea* var. *capitata f. rubra*	109.00-188.00	Cyanidin 3-*O*-diglucoside-5-*O*-glucoside Cyanidin 3-(*ρ*-coumaroyl)-*O*-diglucoside-5-*O*-glucoside Cyanidin 3-(feruloyl)-*O*-diglucoside-5-*O*-glucoside Cyanidin 3-(sinapoyl)-*O*-diglucoside-5-*O*-glucoside	[80,132,133]

			Cyanidin 3-(feruloyl)(feruloyl)-*O*-diglucoside-5-*O*-glucoside	
			Cyanidin 3-(feruloyl)(sinapoyl)-*O*-diglucoside-5-*O*-glucoside	
			Cyanidin 3-(sinapoyl)(sinapoyl)-*O*-diglucoside-5-*O*-glucoside	
Red chicory	*Cichorium intybus*	43.68-72.77	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Cyanidin 3-*O*-(6''malonyl)-glucoside Pelargonidin 3-*O*-glucoside	[134,135]
Red onion	*Allium cepa*	29.99	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-laminaribioside Cyanidin 3-*O*-(3″-malonylglucoside) Peonidin 3-*O*-glucoside Delphinidin 3,5-*O*-diglucoside Cyanidin 3-*O*-(6″-malonylglucoside) Cyanidin 3-*O*-(6″-malonyl-laminaribioside) Peonidin 3-*O*-(6″-malonylglucoside) Delphinidin	[136,137]
Beverages				
Blackberry juice	*Rubus fruticosus*	12.30-107.00	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Cyanidin 3-*O*-xyloside Cyanidin 3-*O*-malonyl-glucoside Cyanidin 3-dioxalylglucoside	[96]
Blueberry juice	*Vaccinium ashei*	317.07-588.87 [3]	Delphinidin 3-*O*-galactoside Delphinidin 3-*O*-glucoside Cyanidin 3-*O*-galactoside Delphinidin 3-*O*-arabinoside Cyanidin 3-*O*-glucoside Petunidin 3-*O*-galactoside Cyanidin 3-*O*-arabinoside Petunidin 3-*O*-glucoside Peonidin 3-*O*-galactoside Petunidin 3-*O*- arabinoside Malvidin 3-*O*-galactoside Malvidin 3-*O*-glucoside Peonidin 3-*O*-arabinoside Malvidin 3-*O*-arabinoside Delphinidin 3-*O*-(6"-acetylglucoside) Petunidin 3-*O*-(6 "-acetylglucoside) Malvidin 3-*O*-(6"-acetylglucoside)	[83,84]
Elderberry juice	*Sambucus nigra*	90.00-5270.00 [3]	Cyanidin 3-*O*-sambubioside-5-*O*-glucoside Cyanidin 3-*O*-sambubioside Cyanidin 3-*O*-glucoside	[81,82,85]
Pomegranate juice	*Punica granatum*	187.00-291.00 [3]	Cyanidin 3-*O*-glucoside Cyanidin 3,5-diglucoside Cyanidin 3-*O*-pentose Cyanidin pentose-hexose Delphinidin 3-*O*-pentose Delphinidin 3,5-diglucoside Pelargonidin 3-*O*-glucoside Pelargonidin 3,5-diglucoside	[86,87,138]
Raspberry juice	*Rubus idaeus*	336.70 [3]	Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-sophoroside Cyanidin 3-*O*-rutinoside Cyanidin 3-*O*-glucorutinoside	[85,139,140]

			Pelargonidin 3-*O*-sophoroside	
			Pelargonidin 3-rutinoside-3'-glucoside	
Red wine	*Vitis vinifera*	52.61-201.60 [3]	Cyanidin 3-*O*-glucoside Delphinidin 3-*O*-glucoside Malvidin 3-(acetyl)glucoside Malvidin 3-O-coumarylglucoside Malvidin 3-O-glucoside Peonidin 3-*O*-glucoside Peonidin 3-(acetyl)glucoside Peonidin 3-*O*-coumarylglucoside Petunidin 3-*O*-glucoside	[85,88,141]
Strawberry juice	*Fragaria × ananassa*	63.60 [3]	Cyanidin 3-*O*-glucoside Pelargonidin-3-*O*-rutinoside Pelargonidin 3-*O*-glucoside	[85,140]
Tart cherry juice	*Prunus cerasus*	350.00-633.50 [3]	Cyanidin Cyanidin 3-*O*-sophoroside Cyanidin 3-*O*-glucosylrutinoside Cyanidin 3-*O*-glucoside Cyanidin 3-*O*-rutinoside Peonidin 3-*O*-rutinoside	[47,77,142]

C3G: cyanidin 3-*O*-glucoside; fw: fresh weight; * mg cyanidin 3-*O*-rutinoside (C3R)/100 g of fw; [1] identified by HPLC technique; [2] identified by HPLC technique (mg/ 100 g dried weight); [3] mg C3G/L.

3.2. Absorption, distribution, metabolism, and excretion (ADME) and bioavailability of anthocyanins

Although there are already some studies on the ADME processes and the bioavailability of anthocyanins, understanding these issues is still a major challenge [143]. However, they are necessary to fully reveal and explore the biological potential of anthocyanins [9,41]. Nowadays, it is believed that the absorption of anthocyanins than the expectable (<28.00%) once anthocyanins undergo extensive metabolism in the colon [33,144–146]. Nevertheless, their percentages are highly variable, depending largely on the individual's sex, genetic profile, age, pre-systemic metabolism, physiological and pathological conditions, dietary habits, lifestyle, intestinal flora, and the presence of possible intolerances, as well as chemical structure, molecular size, glycosylation pattern, and behaviour in the gastrointestinal tract, solubility, transport and permeability [9,147]. For example, pelargonidin aglycone and derivatives are more readily absorbed than other anthocyanins when they have lower substituents on the B ring [148]. Comparing the sugar residues, malvidin 3-*O*-arabinoside shows higher absorption than its 3-*O*-glucoside derivative [149]. In addition, it is important to consider the maturity degree of food matrix and cooking practices can also influence the availability process, as well as their levels and, ability to be released from food matrix, and whether they are administered alone or with other foods and beverages, and/or after a fasting period [41]. Nevertheless, anthocyanins are generally readily absorbed, reaching maximum concentrations ranging from 1.4 to 592 nmol/L (doses of 68-1300 mg) 30 minutes to 4 hours after ingestion [150,151]. The recovery rate in urine is less than 2% 24 hours after ingestion [152].

As mentioned earlier, most anthocyanins found in foods are glycosides [9]. After consumption, anthocyanins are partially degraded by the microbiota in the mouth [153]. They are then passed to the stomach, where the low pH promotes the stability of anthocyanins and their persistence in the form of glycosides [22]. Unlike other flavonoids, anthocyanins can be absorbed along with their sugar moieties [143]. They require the action of bilitranslocase because they are unable to cross cell membranes by passive diffusion due to their hydrophilic nature [49,148]. Therefore, anthocyanins are delivered by bilitranslocase to the portal vein of the liver to be distributed by systemic circulation to target tissues and organs (bioavailability) [148].

However, the majority of anthocyanins ingested in the diet are transported by glucose transporters (GLUT) 1 and 3 to the small intestine, where they are degraded, possibly increasing their absorption and thus bioavailability [41,49]. For this purpose, anthocyanins are deglycosylated in a first step by cytosolic *β*-glucosidase (CGB) in the intestinal lumen and lactase-phloridzin-hydrolase (LPH) in the brush border of intestinal epithelial cells, producing more lipophilic aglycones that are more easily absorbed [144]. Therefore, the released aglycone can enter the intestinal epithelial cells by passive diffusion or via the sodium-dependent transporters GLUT 1 and GLUT 2, metabolic detoxification through phase I (the reactions of hydrolysis, oxidation, and reduction) and phase II enzymatic metabolism (conjugation reactions such as methylation, glucuronidation and sulfation mediated by the enzyme catechol-*O*-methyltransferase, uridine-5′-diphospho-glucuronosyltransferase and sulfotransferase mediated, respectively) [41,143,154]. Similar reactions may also occur in the liver and kidneys [154]. The absorption of the non-acylated anthocyanins is four times higher than that of the acylated ones [155].

The non-absorbed anthocyanins can be excreted in the urine and bile [156] or enter the colon, where they are metabolized by 300-500 different bacteria, mainly of the genera *Bacteroides*, *Bifidobacterium*, *Clostridium* and *Eubacterium*, which convert them to lower molecular-weight compounds, namely phenolic acids, aldehydes, or other phenolics, to increase their absorption [41,144,153]. For example, it has been previously reported that 16 different metabolites derived from the degradation of anthocyanins were identified after the consumption of red raspberries [154]. In addition, 29 different metabolites were detected in the urine of 20 volunteers who had consumed anthocyanin containing beverages including caffeic, *trans*-isoferulic, vanillic, *trans*-ferulic, hippuric, 2,4,6-trihydroxybenzaldehyd and ,4-dihidroxifenilacetic acids derivatives. They peaked 3.5 hours after consumption of the beverage [157]. Moreover, this modulation between colonic bacteria and anthocyanins is very interesting and beneficial because it produces short-chain fatty acids, which together with the new phenolic acids formed, create favourable conditions for the proliferation of probiotic bacteria with remarkable health-promoting properties, such *as Bifidobacteria*, *Actinobacteria* and *Lactobacilli* [158]. So, the conjugated forms may be excreted through bile to jejunum to be then recycled by enteropathic circulation [156]. Unabsorbed anthocyanins are excreted in the stool [33].

Given the great potential of anthocyanins as dietary supplements, several efforts have been made to increase the stability of anthocyanins in the gastrointestinal tract, their absorption and bioavailability, and thus, their biological potential [9]. One of the most promising strategies is the encapsulation of anthocyanins, which will be discussed below [9,48].

4. Anthocyanins in nano-delivery systems

Given the toxicity of many synthetic drugs, the search for and development of new effective drugs is essential [4]. Anthocyanins are a target of many studies in this regard [2,159–163]. However, these phytochemicals are very sensitive to external factors (e.g., pH variations, water, temperature) and have a short half-life [164]. Therefore, it is imperative to develop new delivery systems, that do not exhibit toxicity and are able to increase the stability of anthocyanins and make them kinetically and thermodynamically stable, as well as improve their solubility and pharmaceutical properties [165].

Among the various alternatives studied, those related to nanotechnology and nanoencapsulation have attracted the greatest interest in many fields, such as in medicine, namely in the prevention, diagnosis, and treatment of numerous diseases through active or passive targeting [166–170]. They are preferred over micro-delivery systems because the latter are more unstable in the physiological environment due to their large particle size, low zeta potential, and encapsulation efficiency [171]. Therefore, various approaches to nanoencapsulation are currently being investigated for the different routes of administration, including intravenous, nasal, oral, parenteral, intraocular, and dermal topical applications [172]. In addition, most of them can also easily cross the blood-brain barrier,

which increases the therapeutic potential of the several molecule(s) [170,173]. This technique can be applied because anthocyanins are able to generate van der Waals and hydrogen bonds as well as hydrophobic interactions with these nanocarriers, which increases their stability [24,26,165]. The latter has a particle size between 1 and 1,000 nm and may consist of organic components (e.g., polymer and lipid-based nanoparticles, such as nanoemulsions, liposomes, nanoparticles of solid-lipid), inorganic coatings (e.g., metallic nanostructures, of gold and titanium dioxide, such as nano-quantum dots and nanodiamonds), or a combination of both. Most of them are biodegradable and non-toxic [171,174].

Biopolymers are the most commonly used for nanoencapsulation because they incorporate various types of hydrophobic and hydrophilic molecules (e.g., drugs, proteins, phytochemicals and other molecules), minimizing their undesirable effects and enhancing their benefits [175,176]. Among them, carbohydrates derived from alginate and chitosan, natural gums, and protein derivatives are the most popular [164,177]. They are very effective in encapsulating anthocyanins and contribute greatly to shifting the flavylium cation structure, protecting them from negative environmental effects, thus promoting their stability in the gastrointestinal tract and increasing their bioavailability [20,160,178]. Thus, several studies have already shown that encapsulation of anthocyanins with chitosan and derivatives can improve their physical and oxidative stability, preserve their antioxidant activity, and promote a slower degradation during simulated gastrointestinal digestion and environmental storage [22,27,164,179,180]. Pectin is also considered a promising coating, because of its distinct ability to protect anthocyanins from different pH ranges and temperatures, as well as from damage by ascorbic acid [23,181]. In addition, it promotes a slower release of anthocyanins [182]. Zhao and co-workers [183] developed a nanoliposome of anthocyanins from blueberries coated with pectin and demonstrated a slower release of anthocyanins in simulated gastric fluid (≤ 35.9%), but faster release in simulated intestinal fluid, caused by the degradation of vesicles by the enzyme pancreatin. Liposomal micelles were also found to be effective in increasing the stability and resistance of blueberry anthocyanins in the gastrointestinal tract, resulting in a bioavailability greater than 90% [184]. In addition, the combination of pectin and chitosan has also been a subject of numerous studies. So far, they have already shown a promising ability to protect anthocyanins from degradation by milk and white fluorescent light, as well as from different pH and temperature levels, to maintain their antioxidant capacity, and to improve retention during simulated ingestion and cellular uptake into human Caco-2 intestinal cells [13,28,185]. Similar results were obtained with gum arabic [186,187], α-lactalbumin [48], β-lactoglobulin [2], β-glucan [21], inulin and oligofructose carbohydrates [5], chondroitin sulfate [24], and casein conjugated with carboxymethyl cellulose [160]. The combination of whey protein with glucose also showed a remarkable ability to protect anthocyanins from high temperatures (80 °C) at acidic pH [188], while the use of ovalbumin conjugated with dextran, appears to provide added value for the protection of anthocyanins from hydrogen peroxide-induced oxidative damage, as its conjugation showed a remarkable ability to increase anthocyanins' chemical stability, cellular uptake, and intestinal absorption in human Caco-2 intestinal cells [26]. Peptides are also promising materials for nanoencapsulation. For example, C6M1, a peptide composed of eighteen amino acids, was previously reported to maintain the free radical scavenging ability of cyanidin 3-*O*-glucoside and to be resistant to higher pH values, temperature, and concentrations of metal ions [162]. Apoferritin nanocages exhibit similar capabilities and also showed the ability to facilitate the transport of this anthocyanidin through the cell monolayer of Caco-2 cells [189]. Finally, the use of EUDRAGIT® L100 and polyethylene glycol 2000 can also improve the bioavailability of anthocyanins from açaí berries [190].

Nanoencapsulation involves two primary structures: the first is the nanospheres core structure, in which the polymer matrix is dispersed and/or adsorbed by the bioactive compounds, and the second is the nanocapsule, which may consist of water or oil and a polymer shell [171,191]. When nanoparticles reach the outer cell membrane, they can interact with components of the plasma or extracellular membrane and enter the cell by

endocytosis [26,192,193]. In addition, some biopolymers allow controlled release of the molecules they coated at specific times and cells/organs [9,194].

The most promising *in vitro* and *in vivo* studies on the effects of nanoencapsulated anthocyanins on human health are summarized and discussed below (Figure 4 and Table 2).
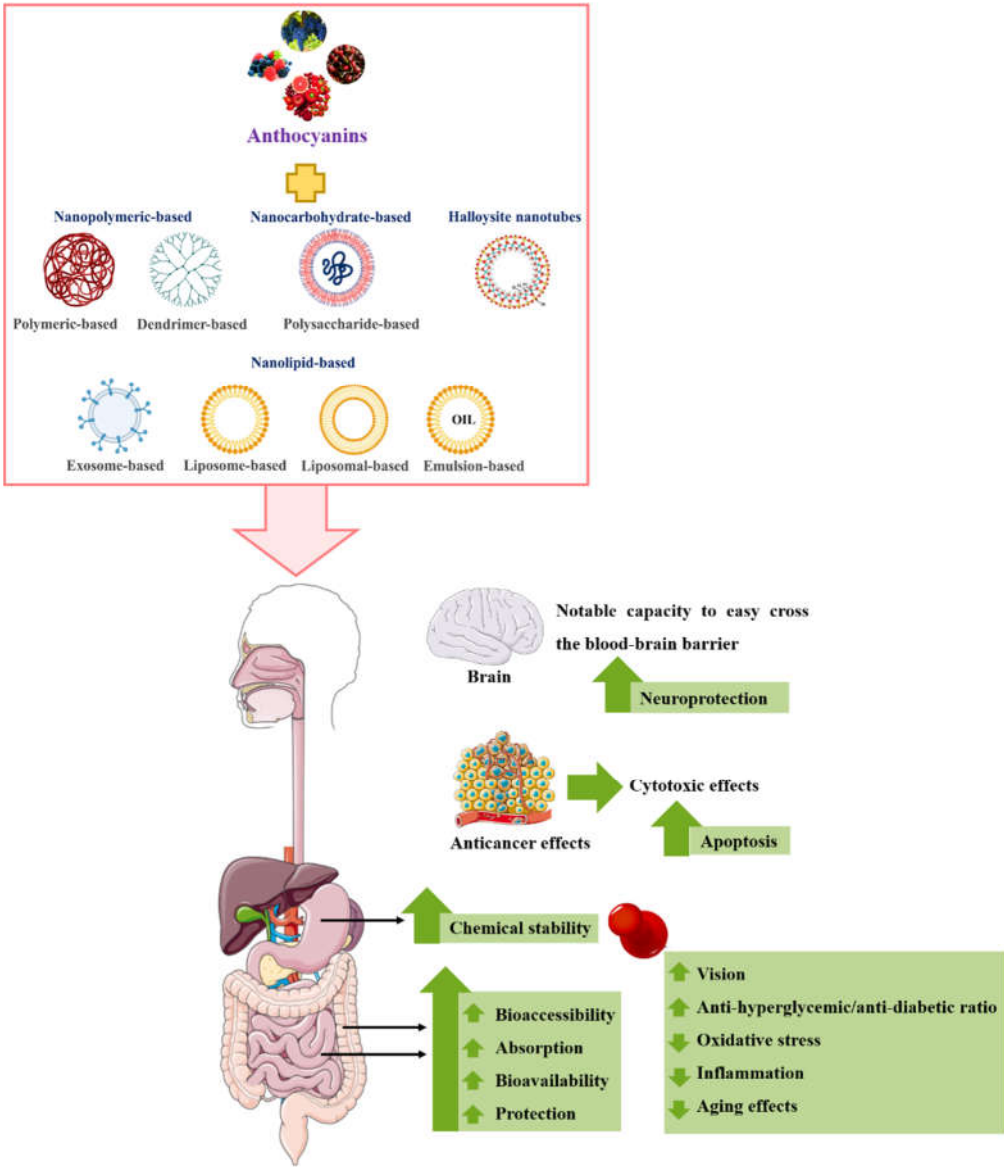

Figure 4. Main *in vitro* and *in vivo* effects of anthocyanins-loaded nanocarriers. ↑: increase; ↓: decrease. (Portions of the figure were drawn using images from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/), BioRender.com (https://biorender.com/) and from Guimarães [195]).

4.1. In vitro studies

4.1.1. Nano-polymeric coatings

The nanoencapsulation of anthocyanins with polymeric coatings has been commonly performed and investigated in *in vitro* conditions [193,196,197]. Among the various options, the use of the synthetic polymer poly(lactic-co-glycolic acid)-acid is very popular because it has tremendous potential to form stable complexes, is non-toxic and biodegradable, and the associated results are highly reproducible worldwide [198]. In addition, they display good tissue penetration and are easy to be manipulated [193]. As far as we

know, this synthetic polymer showed great efficiency in coating pelargonidin, at concentrations of 10, 20 and 30 μM, increasing its ability to inhibit the production of reactive oxygen species in L6 muscle cells exposed to the pesticide cypermethrin, after 12 and 24 hours of exposure [197], as well as protecting these cells from nuclear damage by activating poly(ADP-ribose) polymerase and the p53 pathway, at a concentration of 9 μg/mL [198]. In addition, this coating can also enhance the ability of pelargonidin, at a concentration of 9 μM to reduce the expression of GLUT 4, insulin receptor substrate 1, peptidase inhibitor 3, glycerol kinase and protein kinase and to induce cytochrome complex mediated apoptosis in alloxan-induced hyperglycemic L6 skeletal muscle cells [196]. Moreover, anthocyanins encapsulated with this polymer also showed a higher capacity to protect human neuroblastoma cells SH-SY5Y from neurodegeneration against $A\beta_{1-42}$ induced toxicity than those not encapsulated. Indeed, encapsulated anthocyanins at concentrations between 50 and 200 μM can remarkably reduce Alzheimer's disease markers amyloid precursor protein, beta-site amyloid precursor protein cleaving enzyme, neuroinflammatory markers phospho-nuclear factor kappa B, tumour necrosis factor alpha and inducible nitric oxide synthase after 12 hours of exposure, and the neuroapoptotic markers B-cell lymphoma 2 and associated X-protein (Bax) and caspase-3 protein expressions, and showed notable scavenging properties and ability to abrogate reactive oxygen species production via the p38-MAPK/JNK pathway, as well as increase the expression of endogenous nuclear factor erythroid 2-related factor 2 and heme oxygenase [199].

Nevertheless, it is important to underline that some polymeric coatings can induce allergic reactions and that the complete degradation of some polymeric coatings, such as poly(lactic-co-glycolic acid) in lactic and glycolic acids, takes months, and therefore, their accumulation can lead to disturbances in the microenvironmental pH [199]. Given all, it is urgent to determine the polymer degradation rate and long-term safety of polymeric drug-delivery systems intended for clinical use.

4.1.2. Exosome coatings

Milk exosomes are another promising strategy once they can take on a nanosize and can be easily customised depending on what they encapsulate [200]. Moreover, they are non-toxic, present a reduced immune response, and can confer protection on circulating genetic material, and like other nanoencapsulation coatings, feature remarkable biocompatibility and tumour targeting [201]. In addition, due to their high stability at lower pH values, milk exosomes can be used as carriers for oral drug delivery, enabling a wide range of preventive and therapeutic applications [174]. Recently, Barkallah and colleagues [200] demonstrated that exosomes loaded with 10 μg/mL delphinidin are non-toxic to human aortic endothelial cells, and can correct their nitric oxide levels and reduce angiogenesis, after one day of treatment. Moreover, Aqil and co-workers [201] have previously shown that exosomes in combination with anthocyanins at a concentration of 75 μM increase the potential of these phenolics to arrest the growth of A2780A2780/CP70, OVCA432 and OVCA433 ovarian cancer cells, decrease the P-glycoprotein expression, and reduce the effective cisplatin concentration required to inhibit cisplatin-resistant ovarian cancer cells, after three days of treatment. In addition, exosomes composed of anthocyanins from blueberries also showed higher antiproliferative effects than the unencapsulated anthocyanins on colon cancer cell lines HCT-116 and HT-29 at concentrations between 25 and 200 μM, after 24 hours of treatment [202], and on human lung cells A549 and H1299, breast cells MDA-MB-231 and MCF7, pancreatic cells PANC1 and Mia PaCa2, prostate cells PC3 and DU145, colon cells HCT-116 and ovarian cells OVCA432 at concentrations ranging from 20 to 100 μM, after 72 hours of treatment [174].

Even so, it is important to take into account that exosomes present a limited transfection efficiency.

4.1.3. Nanolipid coatings

The nanoencapsulation of anthocyanins with lipids has also been extensively studied owing to their great biocompatibility, small size, high surface-to-volume ratio and low fusibility [177]. In addition, their synthesis does not require the use of many solvents or aggregation with other nano delivery systems and can be manufactured on large scale with high reproducibility and provide remarkable protection against enzymatic degradation, allowing the creation of a complex with unique physicochemical properties that can deliver the therapeutic molecule directly to target tissues or cells, minimising its concentration and frequency of treatment [192]. The lipid chosen to coat the active molecules depends on many factors, such as the type of bioactive molecules, cosurfactants and surfactants, lipids, and cryoprotectants, as well as the target of the loaded bioactive molecule(s). Nowadays, many studies are focused on nasal delivery of drugs and phytochemicals, e.g., for the treatment of Alzheimer's disease. As far as we know, nanoencapsulation of anthocyanins from elderberries, at a concentration of 0.5 mg/mL, with lipids showed a remarkable ability to modulate mitochondrial functionality, by enhancing complexes I and II of the mitochondrial respiratory chain and preserving the mitochondrial membrane potential in the presence of rotenone thanks to their ability to target mitochondria and protect these cells from rotenone and glutamate-induced toxicity [192].

Recently, lipid-derived nano-niosomes systems, have also attracted considerable attention, because they increase chemical stability and are economical and practical [5]. Anthocyanins encapsulated in niosomes, from black carrots, at concentrations of 6.25 and 100 μg/mL showed the ability to be released after 10 hours, and decrease the viability of neuroblastoma cells Neuro 2A after 2 days of treatment [203], while anthocyanins extracted from *Zea mays* and *Clitoria ternatea* (2-2000 μg/mL) showed a remarkable ability to increase collagen production in human gingival fibroblasts and permeate through the esophageal mucosa [163]. In addition, anthocyanin added nano-niosomes (1%, 2%, 5% and 10%, *v/v*) were reported to be non-toxic to normal HT22 hippocampal neuronal cells, after one day of exposure, and fully internalized in BV2 microglial cells [204].

Even so, one of the major concerns of using lipids as nanocarrier is their cytotoxic potential due to their ability to create non-specific uptake [192].

4.1.4. Nano-polysaccharide coatings

Some types of polysaccharides are also used to encapsulate anthocyanins, as some of them have a charged residue, and therefore, can be easily linked to the opposite charge of the phospholipid residue, thus preventing phospholipid hydrolysis in the presence of enzymes and under acidic pH conditions [13,205]. Among them, chitosan and pectin are the most commonly used because both are non-toxic, environmentally friendly, biodegradable and have high biocompatibility [28]. In addition to their potential advantages, they appear to be a promising, effective drug delivery system to the colon. In *in vitro* studies, nanoencapsulation of anthocyanins at concentrations of 5, 10, 20 and 40 μg/mL with pectin and chitosan showed greater potential to protect normal rat kidney NRK cells from acrylamide-induced damage than non-encapsulated anthocyanins and allowed their controlled release via the gastrointestinal tract [9]. They decreased reactive oxygen species, matrix metalloproteinases, and glutathione levels and provide protection to normal human hepatocyte L02 cells from palmitic acid-induced damage at concentrations ranging from 1.6 to 8.0 μM after 24 hours of exposure [176]. Nevertheless, it is important to emphasize that chitosan dissolves only in certain dilute acidic solutions. Chondroitin sulfate is another promising alternative, as it is able to enhance the ability of black soybean anthocyanins at concentrations of 4, 7.5 and 15 μM to scavenge reactive oxygen species in human colon cells HCT-116 after two days of treatment [206] and to suppress human cervical cancer HeLa cells more effectively compared to anthocyanins alone, both at 100 μM after one day [20]. The combination of chitosan and chondroitin sulfate-loaded black rice anthocyanins at concentrations of 10 and 50 μg/mL also showed remarkable effects on human colon cancer cells HCT-116 by promoting negative changes in mitochondria, and

consequently, apoptosis, after four hours of exposure [207]. Finally, hyaluronic acid, a natural polysaccharide, together with 20 μg/mL cornflower anthocyanins can enhance CD44+ apoptosis in colon cancer cells HT29, after 1 hour of treatment [208].

Even so, the employment of polysaccharide coatings shows some drawbacks, such as their cost, undesirable aggregation, and burst release promoted by their small particle size and large surface [209].

4.1.5. Liposome coatings

Nanoencapsulation of anthocyanins with liposomes has also been investigated, and most studies have already shown that they can be used as nanocarriers for drug delivery due to their self-assembling and amphiphilic properties, flexibility, biocompatibility, biodegradability, longer duration of circulation, and low immunogenicity [183]. In addition, as once they are composed of an aqueous core and a spherical hydrophobic shell, they can transport hydrophilic, hydrophobic, and amphiphilic molecules as well as ease cross the blood-brain barrier [173]. Regarding their encapsulation with anthocyanins, Homayoonfal and colleagues [178] have shown that they can enhance the antioxidant capacity of anthocyanins in a very remarkable and effective manner, as well as increase the metabolite activity and replication of human mesenchymal MSC and fibroblast FBL stem cells, at concentrations of 0.5 mg/mL and 10.4 μg/mL, respectively, after a one-week of treatment. Moreover, it has been also reported that there is a positive correlation between the size of nanoliposome particles and the encapsulation efficiency [161].

Nevertheless, it is important to note that liposomes can trigger undesirable immune responses, present a moderate loading capacity and could crystallize after prolonged storage times [209].

4.1.6. Halloysite nanotubes coatings

The use of halloysite nanotubes is also increasing worldwide, due to their unique properties, such as particle size, high surface area and surface-to-volume ratio, and very high dispersion rate [193]. Regarding anthocyanins, they have shown to be effective to suppress the growth of human breast cancer MCF-7 and human colon cancer HT-29 at a concentration of 500 μg/mL compared to non-encapsulated anthocyanins, after one and two days of exposure [8]. Nonetheless, it is important to consider that halloysite nanotubes are inorganic, presenting toxicity and poor biocompatibility [193].

4.1.7. Dendrimers coatings

Dendrimers are another promising alternative, as they can reduce toxicity and improve water solubility, as well as pharmacokinetic properties and biodistribution [209]. In addition, dendrimers can also be adjusted in size and shape, in order to favor surface area, loading and delivery efficiency. They are usually composed of poly(amidoamine), poly(L-lysine), polyamides, polyethers, polyesters, poly(2,2-bis(hydroxyl methyl) propionic acid and polypropylenimine. Together with anthocyanins, they can increase, dose-dependently, the cytotoxicity of neuro-2A brain neuroblastoma cells, after 24 hours of treatment [194].

However, it is important to note that dendrimers present a complex synthetic route and can only carry low amounts of active molecules.

4.1.8. Nanoemulsions coatings

Nanoemulsions are another interesting drug delivery system, since their production is economic, and show high loading capacity and efficiency to carrier hydrophobic molecules as well as notable capacity to protect bioactive molecules against degradation. In addition, they can be easier manipulated to meliorate drug release. Even so, their use usually requires conjugation with nonionic surfactants to provide better stability [172]. Nonionic are recommended because they are safer than the ionic ones and are usually accepted for oral administration [172]. Recently, Nazareth and coworkers [165] reported

that nanoemulsions of anthocyanins (400–1050 μg/mL) could be a promising alternative to conventional antibiotics. They demonstrated a remarkable ability to inhibit biofilm formation in *Pseudomonas aeruginosa* and *Yersinia enterocolitica*, and anti-quorum sensing activity against *Chromobacterium violaceum*, in a dose-dependent manner.

Nevertheless, it is important not to forget that some nanoemulsions present some non-compatibility, low viscosity and can irritate skin.

4.2. *In vivo studies*

In vivo studies focused on the employment of anthocyanins in nanocarriers for nano delivery are still scarce. Even so, up to date, already exist some reports which showed promising data involving anthocyanins coated with nano-polymeric, dendrimers, carbohydrates, polysaccharides and nano-niosomes, as mentioned below.

4.2.1. Nano-polymeric coatings

However, it has already been reported that the use of polymer-based nanocarriers loaded with anthocyanins, at doses of 0.5 and 1 mg/g body weight. In these conditions, anthocyanins already showed the ability to protect fish models exposed to the pesticide cypermethrin from DNA degradation by increasing the penetrability of anthocyanins in liver, kidney, muscle, brain, and ovarian/testicular tissues and decreasing cytotoxicity by modulating the antioxidant enzymes superoxide dismutase, catalase and lipid peroxidase, after 7 days of treatment [197]. Moreover, complete tumour ablation was verified in MCF-7-bearing nude mice treated with anthocyanins at 250 μg/mL loaded into polymeric nanoparticles, at doses of 0.5 and 1 mg/g body weight after 26 days of treatment [166].

4.2.2. Dendrimers coatings

Anthocyanins encapsulated in exosomes (5 mg anthocyanins and 50 mg exosome protein/kg body weight administered orally by gavage 5 times a week for a period of three 3 weeks) also showed a remarkable ability to reduce tumour size in mice transplanted with A549 human lung cancer cells, with no apparent adverse effects [174]. In addition, they can also reduce the proliferation of colorectal cancer in Apc$^{Min/+}$ mice inoculated with enterotoxigenic *Bacteroides fragilis* bacteria, and treated for 4 weeks, 3 days per week, with a dose of 8.6 mg/kg/day, by increasing the activity phase II enzymes glutathione S-transferase Mu 1 and uridine 5′-diphospho-glucuronosyltransferase family 1 member A6 and decreasing the expression of aryl hydrocarbon receptor nuclear translocator 1, aryl hydrocarbon receptor and cytochrome P450 family 1 subfamily A member 1 [202].

4.2.3. Carbohydrate coatings

Carbohydrate-based derivatives, especially chitosan, have been intensively studied, mainly due to their high loading efficiency, water solubility and biocompatibility [29]. For example, Chatterjee and colleagues [175] reported that the use of anthocyanins loaded with chitosan (at a dose of 600 mg/kg body weight/day) from black carrot gave them the remarkable ability to increase the activity of superoxide dismutase and catalase enzymes in rats. In addition, they can also enhance the potential of cyanidin 3-*O*-glucoside (5 mL/20 g body weight) to attenuate the oxidative stress induced by selenite sodium in rats treated four times daily for one week, enhance the transepithelial transport of liposomes to a depth of 40 mm in the cornea of rats, prolong the residence time on the cornea and improve permeability in the corneal epithelium, thus increasing superoxide dismutase and catalase activity and decreasing glutathione activity and lipid peroxidation in the lens [205]. Moreover, they can also confer to this anthocyanin a higher ability to balance the B-cell lymphoma-2/leukemia-2 ratio and reduce UVB-induced epidermal damage, by decreasing lipid peroxidation, malondialdehyde, and 8-hydroxy-2′-deoxyguanosine and increasing visual and histological appearance and skin hydration, after one day of treatment [210]. In addition, Zhao and colleagues [9] reported that the use of chitosan combined with pectin can provide the ability of blueberry anthocyanins, at a concentration of 320 μg/mL,

to increase the lifespan and reproductive capacity and improve the flexible locomotion behaviour of *Caenorhabditis elegans* from damage induced by acrylamide, heat shock, oxidative stress, and ultraviolet light, and reduce ageing effects.

Even so, one of the major drawbacks of using carbohydrates as nanocarriers is related with their toxicity.

4.2.4. Polysaccharide coatings

On the other hand, the use of polysaccharides nanocarried with anthocyanins from black soybean for 5 days showed efficacy in reducing the tumour size of mice previous injected with human cancer cells HCT-116, increasing the number of apoptotic cells, and also contributing to the release of drugs at target sites [206]. In particular, cornflower anthocyanins loaded into the hyaluronic acid were found to be highly effective in increasing myelosuppression in mice transplanted with human colon cancer cells HT29 and treated for 13 days [208]. In addition, Hafany and coworkers [14] reported that encapsulation of these phytochemicals with bovine serum albumin can ameliorate cardiomyopathy, completely remove glycogen from tissues and reduce malondialdehyde and collagen fibres in fibrotic mouse model treated twice a week for four weeks.

4.2.5. Nano-niosomes coatings

Nano-niosomes are another promising strategy mainly thanks to their non-toxicity, and greater stability, biocompatibility, capacity of penetration and possibility to control and target bioactive molecule(s) delivery [203]. So far, their encapsulation with anthocyanins has already shown remarkable healing activity in oral cavity wounds of rats [163], and ability to improve insulin resistance and glucose intolerance, by increasing the anti-hyperglycemic/anti-diabetic ratios with no apparent toxicity, and lowering animal weight and plasma levels of insulin, glucose, leptin and total cholesterol in obese mice at 300 mg/kg of body weight [4]. Moreover, nanoencapsulation of anthocyanins with nano-niosomes showed pronounced neuroprotection. For example, they can give anthocyanins a remarkable ability to cross the blood-brain barrier, reach it and accumulate in mice with Alzheimer's disease treated for 14 days, thus preventing tau hyperphosphorylation and reducing the expression of amyloid beta, beta-site amyloid precursor protein cleaving enzyme 1 and advanced glycation end products receptor, and neuroinflammatory and oxidative stress markers via the GSK-3β/CDK5 pathway [204]. Moreover, in the $A\beta_{1-42}$ mouse model of Alzheimer's disease, they may enhance the ability of anthocyanins (12 μg/g) to ameliorate memory impairment, as well as protect their pre- and postsynaptic proteins from $A\beta_{1-42}$-induced synaptic dysfunction, regulate the p-PI3K/p-Akt/p-GSK3β pathway, prevent the hyperphosphorylation of tau protein at serines 413 and 404 and inhibited apoptosis during 14 days of treatment [211]. Although they seem to be a hopeful strategy, it is still difficult to find an appropriate concentration able to balance the relationship between the entrapment efficiency and the affinity of the cell membrane.

Even so, the development of nano-niosomes is expensive and exists the risk of aggregation; in addition, nano-niosomes present low loading capacity [163].

Table 2. *In vitro* and *in vivo* studies on the potential therapeutic effects of drug delivery systems nanocarried with anthocyanins.

Source	Nanoencapsulation method	Nanoencapsulating agent(s)	Main achievement	Reference
In vitro studies				
Polymeric-based				
Pelargonidin	Standard solvent displacement technique	Poly(lactic-co-glycolic acid)	■ improved glucose homeostasis signalling cascades by ↓ GLUT4, IRS1, IRS2, PI3, GK and PK protein expression in alloxan-induced hyperglycemic skeletal muscle L6 cells ■ initiated cytochrome complex mediated apoptosis in alloxan-induced hyperglycemic skeletal muscle L6 cells	[196]
Pelargonidin	Displacement technique	Poly(lactic-co-glycolic acid)	↑ L6 muscle cells viability exposed to cypermethrin pesticide, by inhibiting ROS generation ■ protected these cells against nuclear damage	[197]
Pelargonidin	Solvent displacement technique	Poly(lactic-co-glycolic acid)	■ prevented alloxan-induced DNA damage in L6 cells via activation of PARP and p53 and protect them against oxidative stress	[198]
Not mentioned	Emulsification-solvent evaporation technique	Poly(lactic-co-glycolic acid)	■ no cytotoxic effects on human neuroblastoma SH-SY5Y cells ↑ SH-SY5Y cells' viability against Aβ_{1-42} due to their markedly free radical scavenging properties and abrogated reactive oxygen species generation via the p38-MAPK/JNK pathways ↑ induced Nrf2 and HO-1 expression ↓ Alzheimer's markers APP, BACE-1, neuroinflammatory markers ρ-NF-kB, TNF-α and iNOS, and neuroapoptotic markers Bcl2, Bax and caspase-3 protein expressions	[199]
Exosome-based				
Delphinidin	Extracellular vesicles	Small extracellular vesicles from JAWS II cells	■ no cytotoxicity effects on human aortic endothelial cells ■ corrected the levels of nitric oxide in these cells ↓ angiogenesis in these cells	[200]
Anthocyanins from bilberries	Dissolution and mixing methods	Exosomes isolated from mature bovine milk	↓ A2780A2780/CP70, OVCA432 and OVCA433 ovarian cancer cells' growth ↓ P-glycoprotein expression ↓ the dose of cisplatin required to stop the mentioned ovarian cancer cells' growth	[201]
Anthocyanins from bilberries	Dissolution and mixing methods	Exosomes isolated from mature bovine milk	↑ anti-proliferative and anti-inflammatory effects on human lung A549 and H1299, breast MDA-MB-231 and MCF7, pancreatic PANC1 and Mia PaCa2, prostate PC3 and DU145, colon HCT-116 and ovarian OVCA432 cancer cells	[174]
Anthocyanins from bilberries	Dissolution and mixing methods	Exosomes isolated from mature bovine milk	↑ antiproliferative effects on colon HCT-116 and HT-29 cancer cell lines	[202]

			■ no cytotoxicity effects on normal CCD-18Co colon cells	
		Polysaccharide-based		
Pelargonidin 3-*O*-glucoside	Thin-film hydration method combined with probe sonication	Chitosan and pectin	↓ palmitic acid-induced hepatocytes injury in normal human hepatocytes L02 cells by suppressing reactive oxygen production, superoxide generation, MMP collapse ↓ GSH levels	[176]
Anthocyanins from bilberries	Complexation	Chitosan and pectin	↑ storage stability under light and dark conditions ■ improved potential to escape from the interference of stomach acid environment and released slowly in small intestinal fluid, and hence, be delivered in a controlled way along with the gastrointestinal tract ■ protected anthocyanins from degradation by gastric acid ■ protected normal rat kidney NRK cells against acrylamide-induced damage	[9]
Anthocyanins from black soybean	Complexation	Chondroitin sulfate	■ notable potential to scavenge reactive oxygen species in human colon HCT-116 cells	[206]
Anthocyanins from black soybean	Complexation	Chondroitin sulfate	↑ structural stability ■ protected anthocyanins from degradation induced by hydroxyl molecules under pH > 9 ■ suppressed human cervical HeLa cancer cells in a more effective way when compared to anthocyanins alone	[20]
Anthocyanins from black rice	Ionic gelation method	Chitosan and chondroitin sulfate	■ negative changes in mitochondria, by ↑ apoptosis in human colon HCT-116 cancer cells	[207]
		Lipid-based		
Anthocyanins from elderberries	Homogenization, evaporation, sonication and handshaking methods	Lipids from *Codium tomentosum*	■ modulated mitochondria functionality in neuroblastoma SH-SY5Y cells, by ↑ mitochondrial respiratory chain complexes I and II and preserved the mitochondrial membrane potential in the presence of rotenone thanks to their ability to reach mitochondria ■ protected neuroblastoma SH-SY5Y cells against rotenone and glutamate-induced toxicity	[192]
		Nano-niosome gel		
Anthocyanins from *Zea mays* and *Clitoria ternatea*	Thin-film method and hand-shaking methods	Sodium polyacrylate and carbomer 934P (G.M.P.), cholesterol, Span60, fluocinolone acetonide	↑ collagen production in human gingival fibroblasts ↑ permeation through esophageal mucosa	[163]
		Liposome-based		

Anthocyanins from barberries	Combination between hydration and ultrasound processes	Rapeseed lecithin	■ no cytotoxic effects on human mesenchymal MSC and fibroblast FBL stem cells ↑ metabolite activity, cells' replication and antioxidant capacity	[178]
Halloysite nanotubes-based				
Anthocyanins from black carrot	Vacuum	Alumina-silicate sheets	↓ in 2-fold the growth of human breast cancer MCF-7 and human colon cancer HT-29 when compared to non-encapsulated anthocyanins ■ control of anthocyanins' release can be done by pH	[8]
Dendrimer nanoparticles-based				
Anthocyanins from black carrot	Sol-gel technique	Silica-PAMAM dendrimer	↓ cell survival of neuro 2A brain neuroblastoma cells	[194]
Nano-emulsions-based				
Anthocyanins from *Carissa spinarum*	Complexation	Glycerol-sodium benzoate and Tween 80 as surfactant	■ anti-quorum sensing activity against *Chromobacterium violaceum* ■ inhibited biofilm formation in *Pseudomonas aeruginosa* and *Yersinia enterocolitica*	[165]
Anthocyanins from black carrot	Double emulsion method	Polycaprolactone	■ anthocyanins' release after 10 hours ↓ neuroblastoma Neuro 2A cells viability	[203]
Not mentioned	Homogenization, stirring and centrifugation methods	Poly(ethylene glycol)-gold nanoparticles	■ no cytotoxicity effects on normal HT22 hippocampal neuronal cells ■ completely internalization in BV2 microglial cells	[204]
Hyaluronic acid-based				
Anthocyanins from cornflower	Homogenization	Sulfuric hyaluronic acid	■ improved apoptosis of CD44$^+$ in colon cancer HT29 cells	[208]
In vivo studies				
Polymeric-based				
Pelargonidin	Displacement technique	Poly-lactide-co-glycolide acid	↑ penetrability through liver, kidney, muscle, brain, and ovary/testis tissue of fish models exposed cypermethrin pesticide ↓ cytotoxicity in them, by modulating antioxidative enzymes superoxide dismutase, catalase and lipid peroxidase, and hence, protecting fish models against cypermethrin pesticide damage and protecting them against DNA depletion	[197]
Anthocyanins from honeysuckle fruits	One-pot method	Fe^{III} ions and poly(L-glutamic acid)-g-methoxy poly(ethylene glycol)	↑ permeability, retention, and renal clearance ■ complete tumour ablation in MCF-7-bearing nude mice	[166]
Exosomes				

Anthocyanins from bilberries	Dissolution and mixing methods	Exosomes isolated from mature bovine milk	■ significant growth inhibition regarding tumour size in mice that were transplanted with human lung cancer A549 cells, without any apparent undesirable side effects	[174]
Anthocyanins from bilberries	Dissolution and mixing methods	Exosomes isolated from mature bovine milk	↓ colorectal cancer proliferation in Apc$^{Min/+}$ mice inoculated with *Enterotoxigenic Bacteriodes fragilis* bacteria ↓ ARNT1, AhR and CYP1A1 expression in mice ↑ phase II enzymes GSTM1 and UGT1A6	[202]
Carbohydrate-based				
Cyanidin 3-*O*-glycoside	Reverse-phase evaporation method	Chitosan	■ attenuate oxidative stress induced by selenite sodium in rats ■ improved transepithelial transport of liposomes to a depth of 40 mm in the rats' cornea, prolonged residence time on the cornea and ↑ permeability in the corneal epithelium ↑ superoxide dismutase and catalase activity and ↓ glutathione activity and lipid peroxidation in rats' lens	[205]
Cyanidin 3-*O*-glucoside	Ionic gelation	Chitosan and sodium tripolyphosphate	■ slower release at higher pH ■ balanced the B-cell lymphoma-2/leukemia-2 ratio ↓ UVB-induced epidermal damage through the p53-mediated apoptosis signalling pathway, by ↓ UVB-induced lipid peroxidation, malondialdehyde, and 8-hydroxy-2'-deoxyguanosine contents, and downregulate p53, Bax, and caspases- 3 and 9 expressiond ↑ the visual and histologic appearance, skin moisture, and apoptotic index under UVB exposure	[210]
Anthocyanins from bilberries	Complexation	Chitosan and pectin	■ protected *Caenorhabditis elegans* from damage induced by acrylamide, heat shock, oxidative stress, and ultra-violet light ■ complexation ↑ lifespan, reproductive capability and offers a flexible locomotion behaviour in this animal model ■ complexation ↓ autofluorescent lipofuscin particles and exhibit anti-aging effects in this animal model	[9]
Anthocyanins from black carrot	Ionic gelation technique	Chitosan	↑ superoxide dismutase and catalase enzyme activities in rats	[175]
Polysaccharide-based				
Anthocyanins from black soybean	Complexation	Chondroitin sulfate	■ tumour size of mice that were injected with human cancer HCT-116 cells did not change after 5 days of treatment ↑ apoptotic cells ■ tumour targeted and drug released	[206]
Hyaluronic acid-based				

Anthocyanins from cornflower	Homogenization	Sulfuric hyaluronic acid	↓ myelosuppression in mice that were transplanted with colon cancer HT29 cells	[208]
Lipid hybrid-based				
Anthocyanins from red beets	Homogenization	Bovine serum albumin	■ ameliorated cardiomyopathy in fibrotic mice model ■ eliminated glycogen completely from tissue ↓ malondialdehyde and collagen fibers	[14]
Nano-niosome based				
Anthocyanins from *Zea mays* and *Clitoria ternatea*	Thin-film method and hand-shaking methods	Sodium polyacrylate and carbomer 934P (G.M.P.), cholesterol, Span60, fluocinolone acetonide	■ healing activity onto incisional wounds in oral cavities of rats	[163]
Anthocyanins from *Vaccinium Meridionale*	Commercial pronanosome precursor (Nio-N de NANOVEX Biotechnologies S.L, Asturias, España), involving mixture and incubation techniques, and a dispersion using an ultrasound probe	Niosomes	■ ameliorated insulin resistance and glucose intolerance in obese mice ↓ animal weight and plasma insulin, glucose, leptin and total cholesterol levels in them ↑ anti-hyperglycemic/anti-diabetic ratio, without any apparent toxicity	[4]
Not mentioned	Homogenization, stirring and centrifugation methods	Poly (ethylene glycol)-gold nanoparticles	■ coated anthocyanins can successfully cross the blood-brain barrier, reach and be accumulated in Alzheimer's disease mice model ■ prevent tau hyperphosphorylation, and ↓ Amyloid beta, BACE-1, and RAGE expressions, and reduce neuro-inflammatory and oxidative stress markers via GSK-3β/CDK5 pathway	[204]
Antocyanins from from black beans	Dissolution and stirring methods	Polyethylene glycol-with gold nanoparticles	■ ameliorated memory impairments in the Aβ$_{1-42}$ mice model of Alzheimer's disease in a more efficient way than free-anthocyanins ■ protected pre- and postsynaptic proteins from Aβ$_{1-42}$-induced synaptic dysfunction in the Aβ$_{1-42}$-injected mice ■ regulated the p-PI3K/p-Akt/p-GSK3β pathway, preventing the hyperphosphorylation of tau protein at serines 413 and 404 in the Aβ$_{1-42}$- mice model of Alzheimer's disease ■ inhibited apoptosis in the Aβ$_{1-42}$- mice model of Alzheimer's disease	[211]

↑: increase; ↓: decrease; Nrf2: endogenous nuclear factor erythroid 2-related factor 2; HO-1: heme oxygenase 1; BACE-1: beta-site amyloid precursor protein cleaving enzyme 1; RAGE: receptor for advanced glycation end products; APP: amyloid precursor protein; ρ-NF-kB: phospho-nuclear factor kappa B; TNF-α: tumour necrosis factor; iNOS: inducible nitric oxide synthase; Bcl2: B-cell lymphoma 2; Bax: Bcl-2 Associated X-protein; ARNT1: aryl hydrocarbon receptor nuclear translocator 1; AhR: aryl hydrocarbon receptor; CYP1A1: cytochrome P450 Family 1 Subfamily A Member 1; GSTM1: Glutathione S-Transferase Mu 1; UGT1A6: uridine 5'-diphospho-glucuronosyltransferase Family 1 Member A6, GLUT4: Glucose transporter type 4; IRS: Insulin receptor substrate; PI3: Peptidase Inhibitor 3; GK: glycerol kinase; PK: protein kinase; MMP: matrix metalloproteinases; GSH: Glutathione; PARP: poly(ADP-ribose) polymerase; PAMAM: poly(amidoamine).

5. Conclusions

Given the worldwide increase in chronic diseases and the urgent need to search for new, effective, safe and low-toxicity drugs, it is not surprising that many phytochemicals, such as anthocyanins, are considered good candidates. In fact, their pyrogallol, methoxy, and catechol groups confer remarkable health-promoting properties to anthocyanins. Therefore, and considering their limitations (e.g., high sensitivity to pH, rapid absorption and metabolization), the encapsulation seems to be a promising approach. Nevertheless, it is imperative to know their safe dosage in humans, since they may act as pro-oxidants under certain conditions, and because, in many situations, the use of higher dosages may not help to increase their biological potential. In addition, combination with other bioactive molecules/pharmaceuticals also appears to be a promising strategy.

Author Contributions: Ana C. Gonçalves: Conceptualization, Data curation, Formal analysis, Writing- original draft; Luís R. Silva, João Lopes: Conceptualization and Writing- review & editing; Luís R. Silva, Gilberto Alves, Amílcar Falcão and João Lopes: Conceptualization, Funding acquisition, Project administration, Supervision, Writing- review & editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Norcino, L.B.; Mendes, J.F.; Figueiredo, J. de A.; Oliveira, N.L.; Botrel, D.A.; Mattoso, L.H.C. Development of alginate/pectin microcapsules by a dual process combining emulsification and ultrasonic gelation for encapsulation and controlled release of anthocyanins from grapes (*Vitis labrusca* L.). *Food Chem.* **2022**, *391*, doi:10.1016/j.foodchem.2022.133256.
2. Salah, M.; Mansour, M.; Zogona, D.; Xu, X. Nanoencapsulation of anthocyanins-loaded *β*-lactoglobulin nanoparticles: Characterization, stability, and bioavailability *in vitro*. *Food Res. Int.* **2020**, *137*, 109635, doi:10.1016/j.foodres.2020.109635.
3. Ballesteros, L.F.; Ramirez, M.J.; Orrego, C.E.; Teixeira, J.A.; Mussatto, S.I. Encapsulation of antioxidant phenolic compounds extracted from spent coffee grounds by freeze-drying and spray-drying using different coating materials. *Food Chem.* **2017**, *237*, 623–631, doi:10.1016/j.foodchem.2017.05.142.
4. Colorado, D.; Fernandez, M.; Orozco, J.; Lopera, Y.; Muñoz, D.L.; Acín, S.; Balcazar, N. Metabolic activity of anthocyanin extracts loaded into non-ionic niosomes in diet-induced obese mice. *Pharm. Res.* **2020**, *37*, doi:10.1007/s11095-020-02883-z.
5. Figueiredo, J. de A.; Teixeira, M.A.; Campelo, P.H.; Lago, A.M.T.; Souza, T.P. de; Yoshida, M.I.; Oliveira, C.R. de; Pereira, A.P.A.; Pastore, G.M.; Sanches, E.A.; Botrel, D.A.; Borges, S.V. Encapsulation of camu-camu extracts using prebiotic biopolymers: Controlled release of bioactive compounds and effect on their physicochemical and thermal properties. *Food Res. Int.* **2020**, *137*, 109563, doi:10.1016/j.foodres.2020.109563.
6. Nisar, A. Medicinal plants and phenolic compounds. In *Phenolic Compounds - Chemistry, Synthesis, Diversity, Non-Conventional Industrial, Pharmaceutical and Therapeutic Applications*; Badria, F., Ed.; IntechOpen: London, United Kingdom, 2022; p. 13.
7. Ulriksen, E.S.; Butt, H.S.; Ohrvik, A.; Blakeney, R.A.; Kool, A.; Wangensteen, H.; Inngjerdingen, M.; Inngjerdingen, K.T. The discovery of novel immunomodulatory medicinal plants by combination of historical text reviews and immunological screening assays. *J. Ethnopharmacol.* **2022**, *296*, 115402, doi:10.1016/j.jep.2022.115402.
8. Hamedi, S.; Koosha, M. Designing a pH-responsive drug delivery system for the release of black-carrot anthocyanins loaded in halloysite nanotubes for cancer treatment. *Appl. Clay Sci.* **2020**, *197*, 105770, doi:10.1016/j.clay.2020.105770.
9. Zhao, X.; Zhang, X.; Tie, S.; Hou, S.; Wang, H.; Song, Y.; Rai, R.; Tan, M. Facile synthesis of nano-nanocarriers from chitosan and pectin with improved stability and biocompatibility for anthocyanins delivery: An in vitro and in vivo study. *Food Hydrocoll.* **2020**, *109*, 106114, doi:10.1016/j.foodhyd.2020.106114.
10. Gonçalves, A.C.; Flores-Félix, D.; Costa, A.R.; Falcão, A.; Alves, G.; Silva, L.R. Hepatoprotective effects of sweet cherry extracts (cv. Saco). *Foods* **2021**, *10*, 2623.
11. Gonçalves, A.C.; Rodrigues, M.; Santos, A.O.; Alves, G.; Silva, L.R. Antioxidant status, antidiabetic properties and effects on Caco-2 cells of colored and non-colored enriched extracts of sweet cherry fruits. *Nutrients* **2018**, *10*, 1688, doi:10.3390/nu10111688.
12. Gonçalves, A.C.; Costa, A.R.; Flores-Félix, J.D.; Alves, G.; Silva, L.R. Anti-inflammatory and antiproliferative properties of sweet cherry phenolic-rich extracts. *Molecules* **2022**, *27*, 268.

13. Sun, Y.; Chi, J.; Ye, X.; Wang, S.; Liang, J.; Yue, P.; Xiao, H.; Gao, X. Nanoliposomes as delivery system for anthocyanins: Physicochemical characterization, cellular uptake, and antioxidant properties. *LWT* **2021**, *139*, 110554, doi:10.1016/j.lwt.2020.110554.

14. Hanafy, N.A.N. Starch based hydrogel NPs loaded by anthocyanins might treat glycogen storage at cardiomyopathy in animal fibrotic model. *Int. J. Biol. Macromol.* **2021**, *183*, 171–181, doi:10.1016/j.ijbiomac.2021.04.131.

15. Cai, X.Y.; Yang, C.; Shao, L.; Zhu, H.M.; Wang, Y.X.; Huang, X.; Wang, S.; Hong, L. Targeting NOX 4 by petunidin improves anoxia/reoxygenation-induced myocardium injury. *Eur. J. Pharmacol.* **2020**, *888*, 173414, doi:10.1016/j.ejphar.2020.173414.

16. Zhou, L.; Wang, H.; Yi, J.; Yang, B.; Li, M.; He, D.; Yang, W.; Zhang, Y.; Ni, H. Anti-tumor properties of anthocyanins from Lonicera caerulea 'Beilei' fruit on human hepatocellular carcinoma: in vitro and in vivo study. *Biomed. Pharmacother.* **2018**, *104*, 520–529, doi:10.1016/j.biopha.2018.05.057.

17. Lazzè, M.C.; Savio, M.; Pizzala, R.; Cazzalini, O.; Perucca, P.; Scovassi, A.I.; Stivala, L.A.; Bianchi, L. Anthocyanins induce cell cycle perturbations and apoptosis in different human cell lines. *Carcinogenesis* **2004**, *25*, 1427–1433, doi:10.1093/carcin/bgh138.

18. Ma, T.; Hu, N.; Ding, C.; Zhang, Q.; Li, W.; Suo, Y.; Wang, H.; Bai, B.; Ding, C. *In vitro* and *in vivo* biological activities of anthocyanins from Nitraria tangutorun Bobr. fruits. *Food Chem.* **2016**, *194*, 296–303, doi:10.1016/j.foodchem.2015.07.110.

19. Rahman, S.; Mathew, S.; Nair, P.; Ramadan, W.S.; Vazhappilly, C.G. Health benefits of cyanidin-3-glucoside as a potent modulator of Nrf2-mediated oxidative stress. *Inflammopharmacology* **2021**, *29*, 907–923, doi:10.1007/s10787-021-00799-7.

20. Jeong, D.; Na, K. Chondroitin sulfate based nanocomplex for enhancing the stability and activity of anthocyanin. *Carbohydr. Polym.* **2012**, *90*, 507–515, doi:10.1016/j.carbpol.2012.05.072.

21. Ahmad, M.; Ashraf, B.; Gani, A.; Gani, A. Microencapsulation of saffron anthocyanins using β glucan and β cyclodextrin: Microcapsule characterization, release behaviour & antioxidant potential during in-vitro digestion. *Int. J. Biol. Macromol.* **2018**, *109*, 435–442, doi:10.1016/j.ijbiomac.2017.11.122.

22. Shi, M.; Bai, J.; Zhao, L.; Yu, X.; Liang, J.; Liu, Y.; Nord, W.; Li, Y. Co-loading and intestine-specific delivery of multiple antioxidants in pH-responsive microspheres based on TEMPO-oxidized polysaccharides. *Carbohydr. Polym.* **2017**, *157*, 858–865, doi:10.1016/j.carbpol.2016.10.057.

23. Arroyo-Maya, I.J.; McClements, D.J. Biopolymer nanoparticles as potential delivery systems for anthocyanins: Fabrication and properties. *Food Res. Int.* **2015**, *69*, 1–8, doi:10.1016/j.foodres.2014.12.005.

24. Tan, C.; Selig, M.J.; Lee, M.C.; Abbaspourrad, A. Polyelectrolyte microcapsules built on $CaCO_3$ scaffolds for the integration, encapsulation, and controlled release of copigmented anthocyanins. *Food Chem.* **2018**, *246*, 305–312, doi:10.1016/j.foodchem.2017.11.033.

25. Nogueira, G.F.; Soares, C.T.; Martin, L.G.P.; Fakhouri, F.M.; de Oliveira, R.A. Influence of spray drying on bioactive compounds of blackberry pulp microencapsulated with arrowroot starch and gum arabic mixture. *J. Microencapsul.* **2020**, *37*, 65–76, doi:10.1080/02652048.2019.1693646.

26. Feng, J.; Wu, Y.; Zhang, L.; Li, Y.; Liu, S.; Wang, H.; Li, C. Enhanced chemical stability, intestinal absorption, and intracellular antioxidant activity of cyanidin-3- O-glucoside by composite nanogel encapsulation. *J. Agric. Food Chem.* **2019**, *67*, 10432–10447, doi:10.1021/acs.jafc.9b04778.

27. He, B.; Ge, J.; Yue, P.; Yue, X.Y.; Fu, R.; Liang, J.; Gao, X. Loading of anthocyanins on chitosan nanoparticles influences anthocyanin degradation in gastrointestinal fluids and stability in a beverage. *Food Chem.* **2017**, *221*, 1671–1677, doi:10.1016/j.foodchem.2016.10.120.

28. Shishir, M.R.I.; Karim, N.; Xie, J.; Rashwan, A.K.; Chen, W. Colonic delivery of pelargonidin-3-O-glucoside using pectin-chitosan-nanoliposome: Transport mechanism and bioactivity retention. *Int. J. Biol. Macromol.* **2020**, *159*, 341–355, doi:10.1016/j.ijbiomac.2020.05.076.

29. Nguyen, Q.D.; Dang, T.T.; Nguyen, T.V.L.; Nguyen, T.T.D.; Nguyen, N.N. Microencapsulation of roselle (*Hibiscus sabdariffa* L.) anthocyanins: Effects of different carriers on selected physicochemical properties and antioxidant activities of spray-dried and freeze-dried powder. *Int. J. Food Prop.* **2022**, *25*, 359–374, doi:10.1080/10942912.2022.2044846.

30. Go, E.J.; Ryu, B.R.; Ryu, S.J.; Kim, H.B.; Lee, H.T.; Kwon, J.W.; Baek, J.S.; Lim, J.D. An enhanced water solubility and stability of anthocyanins in mulberry processed with hot melt extrusion. *Int. J. Mol. Sci.* **2021**, *22*, doi:10.3390/ijms222212377.

31. Pismenskaya, N.; Sarapulova, V.; Klevtsova, A.; Mikhaylin, S.; Bazinet, L. Adsorption of anthocyanins by cation and anion exchange resins with aromatic and aliphatic polymer matrices. *Int. J. Mol. Sci.* **2020**, *21*, 1–26, doi:10.3390/ijms21217874.

32. Willemse, C.M.; Stander, M.A.; de Villiers, A. Hydrophilic interaction chromatographic analysis of anthocyanins. *J. Chromatogr. A* **2013**, *1319*, 127–140, doi:10.1016/j.chroma.2013.10.045.

33. Zhong, S.; Sandhu, A.; Edirisinghe, I.; Burton-Freeman, B. Characterization of wild blueberry polyphenols bioavailability and kinetic profile in plasma over 24-h period in human subjects. *Mol. Nutr. Food Res.* **2017**, *61*, 1–13, doi:10.1002/mnfr.201700405.

34. Clifford, M.N. Anthocyanins - Nature, occurrence and dietary burden. *J. Sci. Food Agric.* **2000**, *80*, 1063–1072, doi:10.1002/(SICI)1097-0010(20000515)80:7<1063::AID-JSFA605>3.0.CO;2-Q.

35. Wu, X.; Prior, R.L. Identification and characterization of anthocyanins by high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry in common foods in the United States: Vegetables, nuts, and grains. *J. Agric. Food Chem.* **2005**, *53*, 3101–3113, doi:10.1021/jf0478861.

36. Kähkönen, M.P.; Heinonen, M. Antioxidant activity of anthocyanins and their aglycons. *J. Agric. Food Chem.* **2003**, *51*, 628–633, doi:10.1021/jf025551i.

37. Cabrita, L.; Fossen, T.; Andersen, M. Analytical, nutritional and clinical methods section colour and stability of the six common anthocyanidin 3-glucosides in aqueous solutions. *Food Chem.* **2000**, *68*, 101–107.

38. Akita, Y.; Kitamura, S.; Hase, Y.; Narumi, I.; Ishizaka, H.; Kondo, E.; Kameari, N.; Nakayama, M.; Tanikawa, N.; Morita, Y.; Tanaka, A. Isolation and characterization of the fragrant cyclamen *O*-methyltransferase involved in flower coloration. *Planta* **2011**, *234*, 1127–1136, doi:10.1007/s00425-011-1466-0.

39. Singla, R.K.; Dubey, A.K.; Garg, A.; Sharma, R.K.; Fiorino, M.; Ameen, S.M.; Haddad, M.A.; Al-Hiary, M. Natural polyphenols: Chemical classification, definition of classes, subcategories, and structures. *J. AOAC Int.* **2019**, *102*, 1397–1400, doi:10.5740/jaoacint.19-0133.

40. Wahyuningsih, S.; Wulandari, L.; Wartono, M.W.; Munawaroh, H.; Ramelan, A.H. The effect of pH and color stability of anthocyanin on food colorant. *IOP Conf. Ser. Mater. Sci. Eng.* **2017**, *193*, doi:10.1088/1757-899X/193/1/012047.

41. Mueller, D.; Jung, K.; Winter, M.; Rogoll, D.; Melcher, R.; Richling, E. Human intervention study to investigate the intestinal accessibility and bioavailability of anthocyanins from bilberries. *Food Chem.* **2017**, *231*, 275–286, doi:10.1016/j.foodchem.2017.03.130.

42. Nhut Pham, T.; Quoc Toan, T.; Duc Lam, T.; Vu-Quang, H.; Vo, D.V.N.; Anh Vy, T.; Bui, L.M. Anthocyanins extraction from Purple Sweet Potato (*Ipomoea batatas* (L.) Lam): The effect of pH values on natural color. *IOP Conf. Ser. Mater. Sci. Eng.* **2019**, *542*, doi:10.1088/1757-899X/542/1/012031.

43. Torskangerpoll, K.; Andersen, Ø.M. Colour stability of anthocyanins in aqueous solutions at various pH values. *Food Chem.* **2005**, *89*, 427–440, doi:10.1016/j.foodchem.2004.03.002.

44. Pina, F.; Oliveira, J.; De Freitas, V. Anthocyanins and derivatives are more than flavylium cations. *Tetrahedron* **2015**, *71*, 3107–3114, doi:10.1016/j.tet.2014.09.051.

45. Ibrahim, U.K.; Muhammad, I.I.; Salleh, R.M. The effect of pH on color behavior of Brassica oleracea anthocyanin. *J. Appl. Sci.* 2011, *11*, 2406–2410.

46. Marhuenda, J.; Alemán, M.D.; Gironés-Vilaplana, A.; Pérez, A.; Caravaca, G.; Figueroa, F.; Mulero, J.; Zafrilla, P. Phenolic composition, antioxidant activity, and in vitro availability of four different berries. *J. Chem.* **2016**, *2016*, doi:10.1155/2016/5194901.

47. Wojdyło, A.; Nowicka, P.; Teleszko, M. Degradation kinetics of anthocyanins in sour cherry cloudy juices at different storage temperature. *Processes* **2019**, *7*, 1–14, doi:10.3390/pr7060367.

48. Jiang, P.; Huang, J.; Bao, C.; Jiao, L.; Zhao, H.; Du, Y.; Fazheng, R.; Li, Y. Enzymatically partially hydrolyzed α-Lactalbumin peptides for self-assembled micelle formation and their application for coencapsulation of multiple antioxidants. *J. Agric. Food Chem.* **2018**, *66*, 12921–12930, doi:10.1021/acs.jafc.8b03798.

49. Oliveira, H.; Roma-Rodrigues, C.; Santos, A.; Veigas, B.; Brás, N.; Faria, A.; Calhau, C.; de Freitas, V.; Baptista, P. V.; Mateus, N.; Fernandes, A.R.; Fernandes, I. GLUT1 and GLUT3 involvement in anthocyanin gastric transport- Nanobased targeted approach. *Sci. Rep.* **2019**, *9*, 1–14, doi:10.1038/s41598-018-37283-2.

50. Zamora-Ros, R.; Knaze, V.; Luján-Barroso, L.; Slimani, N.; Romieu, I.; Touillaud, M.; Kaaks, R.; Teucher, B.; Mattiello, A.; Grioni, S.; Crowe, V.; Boeing, H.; Förster, J.; Quirós, R.; Molina, E.; Huerta,J.M.; Engeset, D.; Skeie, G.; Trichopoulou, A., Dilis, V.; Tsiotas, K.; Peeters, P.H.M.; Khaw, K.T.; Wareham, N.; Bueno-de-Mesquita, B.; Ocké, M.C.; Olsen, A.; Tjønneland, A.; Tumino, R.; Johansson, G.; Johansson, I.; Ardanaz, E.; Sacerdote, C.; Sonestedt, E.; Ericson, U.; Clavel-Chapelon, F.; Boutron-Ruault, M.C.; Fagherazzi, G.; Salvini, S.; Amiano, P.; Riboli, E.; González, C.A. Estimation of the intake of anthocyanidins and their food sources in the European prospective investigation into cancer and nutrition (EPIC) study. *Br. J. Nutr.* **2011**, *106*, 1090–1099, doi:10.1017/S0007114511001437.

51. Wu, X.; Beecher, G.R.; Holden, J.M.; Haytowitz, D.B.; Gebhardt, S.E.; Prior, R.L. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. *J. Agric. Food Chem.* **2006**, *54*, 4069–4075, doi:10.1021/jf060300l.

52. Kim, K.; Vance, T.M.; Chun, O.K. Estimated intake and major food sources of flavonoids among US adults: changes between 1999–2002 and 2007–2010 in NHANES. *Eur. J. Nutr.* **2016**, *55*, 833–843, doi:10.1007/s00394-015-0942-x.

53. Cremonini, E.; Daveri, E.; Iglesias, D.E.; Kang, J.; Wang, Z.; Gray, R.; Mastaloudis, A.; Kay, C.D.; Hester, S.N.; Wood, S.M.; Fraga, C.G.; Oteiza, P.I. A randomized placebo-controlled cross-over study on the effects of anthocyanins on inflammatory and metabolic responses to a high-fat meal in healthy subjects. *Redox Biol.* **2022**, *51*, 102273, doi:10.1016/j.redox.2022.102273.

54. Krikorian, R.; Skelton, M.R.; Summer, S.S.; Shidler, M.D.; Sullivan, P.G. Blueberry supplementation in midlife for dementia risk reduction. *Nutrients* **2022**, *14*, 1619.

55. Matta, F. V.; Xiong, J.; Lila, M.A.; Ward, N.I.; Felipe-Sotelo, M.; Esposito, D. Chemical composition and bioactive properties of commercial and non-commercial purple and white açaí berries. *Foods* **2020**, *9*, 1–17, doi:10.3390/foods9101481.

56. Vera de Rosso, V.; Hillebrand, S.; Cuevas Montilla, E.; Bobbio, F.O.; Winterhalter, P.; Mercadante, A.Z. Determination of anthocyanins from acerola (*Malpighia emarginata* DC.) and açai (*Euterpe oleracea* Mart.) by HPLC-PDA-MS/MS. *J. Food Compos. Anal.* **2008**, *21*, 291–299, doi:10.1016/j.jfca.2008.01.001.

57. Lohachoompol, V.; Mulholland, M.; Srzednicki, G.; Craske, J. Determination of anthocyanins in various cultivars of highbush and rabbiteye blueberries. *Food Chem.* **2008**, *111*, 249–254, doi:10.1016/j.foodchem.2008.03.067.

58. Bunea, A.; Rugină, D.O.; Pintea, A.M.; Sconţa, Z.; Bunea, C.I.; Socaciu, C. Comparative polyphenolic content and antioxidant activities of some wild and cultivated blueberries from Romania. *Not. Bot. Horti Agrobot. Cluj-Napoca* **2011**, *39*, 70–76, doi:10.15835/nbha3926265.

59. Guofang, X.; Xiaoyan, X.; Xiaoli, Z.; Yongling, L.; Zhibing, Z. Changes in phenolic profiles and antioxidant activity in rabbiteye blueberries during ripening. *Int. J. Food Prop.* **2019**, *22*, 320–329, doi:10.1080/10942912.2019.1580718.

60. Sellappan, S.; Akoh, C.C.; Krewer, G. Phenolic compounds and antioxidant capacity of Georgia-grown blueberries and blackberries. *J. Agric. Food Chem.* **2002**, *50*, 2432–2438, doi:10.1021/jf011097r.

61. Müller, D.; Schantz, M.; Richling, E. High performance liquid chromatography analysis of anthocyanins in bilberries (*Vaccinium myrtillus* L.), blueberries (*Vaccinium corymbosum* L.), and corresponding juices. *J. Food Sci.* **2012**, *77*, 1–6, doi:10.1111/j.1750-3841.2011.02605.x.

62. Martín-Gómez, J.; Varo, M.Á.; Mérida, J.; Serratosa, M.P. Influence of drying processes on anthocyanin profiles, total phenolic compounds and antioxidant activities of blueberry (*Vaccinium corymbosum*). *Lwt* **2020**, *120*, 108931, doi:10.1016/j.lwt.2019.108931.

63. Becker Pertuzatti, P.; Teixeira Barcia, M.; Gómez-Alonso, S.; Teixeira Godoy, H.; Hermosin-Gutierrez, I. Phenolics profiling by HPLC-DAD-ESI-MSn aided by principal component analysis to classify rabbiteye and highbush blueberries. *Food Chem.* **2021**, *340*, 127958, doi:10.1016/j.foodchem.2020.127958.

64. Ferreira, S.S.; Silva, P.; Silva, A.M.; Nunes, F.M. Effect of harvesting year and elderberry cultivar on the chemical composition and potential bioactivity: A three-year study. *Food Chem.* **2020**, *302*, doi:10.1016/j.foodchem.2019.125366.

65. Zheng, W.; Wang, S.Y. Oxygen radical absorbing capacity of phenolics in blueberries, cranberries, chokeberries, and lingonberries. *J. Agric. Food Chem.* **2003**, *51*, 502–509, doi:10.1021/jf020728u.

66. Du, B.; He, B.-J.; Shi, P.-B.; Li, F.-Y.; Li, J.; Zhu, F. Phenolic content and antioxidant activity of wine grapes and table grapes. *J. Med. Plants Res.* **2012**, *6*, 3381–3387, doi:10.5897/jmpr12.238.

67. Kolarov, R.; Tukuljac, M.P.; Kolbas, A.; Kolbas, N.; Barać, G.; Ognjanov, V.; Ljubojević, M.; Prvulović, D. Antioxidant capacity of wild-growing bilberry, elderberry, and strawberry fruits. *Acta Hortic. Regiotect.* **2021**, *24*, 119–126, doi:10.2478/ahr-2021-0033.

68. Borowiec, K.; Stachniuk, A.; Szwajgier, D.; Trzpil, A. Polyphenols composition and the biological effects of six selected small dark fruits. *Food Chem.* **2022**, *391*, 133281, doi:10.1016/j.foodchem.2022.133281.

69. Mullen, W.; Lean, M.E.J.; Crozier, A. Rapid characterization of anthocyanins in red raspberry fruit by high-performance liquid chromatography coupled to single quadrupole mass spectrometry. *J. Chromatogr. A* **2002**, *966*, 63–70, doi:10.1016/S0021-9673(02)00699-4.

70. Chen, F.; Sun, Y.; Zhao, G.; Liao, X.; Hu, X.; Wu, J.; Wang, Z. Optimization of ultrasound-assisted extraction of anthocyanins in red raspberries and identification of anthocyanins in extract using high-performance liquid chromatography-mass spectrometry. *Ultrason. Sonochem.* **2007**, *14*, 767–778, doi:10.1016/j.ultsonch.2006.12.011.

71. Gonçalves, A.C.; Rodrigues, M.; Flores-Félix, J.D.; Nunes, A.R.; Ribeiro, A.B.; Alves, G. Sweet cherry phenolics revealed to be promising agents in inhibiting P-glycoprotein activity and increasing cellular viability under oxidative stress conditions : in vitro and in silico study. *J. Food Sci.* **2021**, doi:10.1111/1750-3841.16001.

72. Picariello, G.; De Vito, V.; Ferranti, P.; Paolucci, M.; Volpe, M.G. Species- and cultivar-dependent traits of *Prunus avium* and *Prunus cerasus* polyphenols. *J. Food Compos. Anal.* **2016**, *45*, 50–57, doi:10.1016/j.jfca.2015.10.002.

73. Mulabagal, V.; Lang, G.A.; Dewitt, D.L.; Dalavoy, S.S.; Nair, M.G. Anthocyanin content, lipid peroxidation and cyclooxygenase enzyme inhibitory activities of sweet and sour cherries. *J. Agric. Food Chem.* **2009**, *57*, 1239–1246, doi:10.1021/jf8032039.

74. Gonçalves, A.C.; Campos, G.; Alves, G.; Garcia-Viguera, C.; Moreno, D.A.; Silva, L.R. Physical and phytochemical composition of 23 Portuguese sweet cherries as conditioned by variety (or genotype). *Food Chem.* **2021**, *335*, 127637, doi:10.1016/j.foodchem.2020.127637.

75. Martini, S.; Conte, A.; Tagliazucchi, D. Phenolic compounds profile and antioxidant properties of six sweet cherry (*Prunus avium*) cultivars. *Food Res. Int.* **2017**, *97*, 15–26, doi:10.1016/j.foodres.2017.03.030.

76. Kim, D.O.; Ho, J.H.; Young, J.K.; Hyun, S.Y.; Lee, C.Y. Sweet and sour cherry phenolics and their protective effects on neuronal cells. *J. Agric. Food Chem.* **2005**, *53*, 9921–9927, doi:10.1021/jf0518599.

77. Kirakosyan, A.; Seymour, E.M.; Llanes, D.E.U.; Kaufman, P.B.; Bolling, S.F. Chemical profile and antioxidant capacities of tart cherry products. *Food Chem.* **2009**, *115*, 20–25, doi:10.1016/j.foodchem.2008.11.042.

78. Colak, N.; Kurt-Celebi, A.; Gruz, J.; Strnad, M.; Hayirlioglu-Ayaz, S.; Choung, M.G.; Esatbeyoglu, T.; Ayaz, F.A. The phenolics and antioxidant properties of black and purple versus white eggplant cultivars. *Molecules* **2022**, *27*, doi:10.3390/molecules27082410.

79. Li, J.; Li, X.D.; Zhang, Y.; Zheng, Z.D.; Qu, Z.Y.; Liu, M.; Zhu, S.H.; Liu, S.; Wang, M.; Qu, L. Identification and thermal stability of purple-fleshed sweet potato anthocyanins in aqueous solutions with various pH values and fruit juices. *Food Chem.* **2013**, *136*, 1429–1434, doi:10.1016/j.foodchem.2012.09.054.

80. Wiczkowski, W.; Szawara-Nowak, D.; Topolska, J. Red cabbage anthocyanins: Profile, isolation, identification, and antioxidant activity. *Food Res. Int.* **2013**, *51*, 303–309, doi:10.1016/j.foodres.2012.12.015.

81. Wu, H.; Johnson, M.C.; Lu, C.H.; Fritsche, K.L.; Thomas, A.L.; Cai, Z.; Greenlief, C.M. Determination of anthocyanins and total polyphenols in a variety of elderberry juices by UPLC-MS/MS and Other Methods. *Acta Hortic.* **2015**, *1061*, 43–52, doi:10.17660/actahortic.2015.1061.3.

82. Silva, R.F.R. da; João C. M. Barreira; Heleno, S.A.; Barros, L.; Calhelha, R.C.; Ferreira, I.C.F.R. Anthocyanin profile of elderberry juice: Potential food application. *Molecules* **2019**, *24*, 2359–2372.

83. Zhang, L.; Wu, G.; Wang, W.; Yue, J.; Yue, P.; Gao, X. Anthocyanin profile, color and antioxidant activity of blueberry (*Vaccinium ashei*) juice as affected by thermal pretreatment. *Int. J. Food Prop.* **2019**, *22*, 1036–1046, doi:10.1080/10942912.2019.1625366.

84. Howard, L.R.; Brownmiller, C.; Mauromoustakos, A.; Prior, R.L. Improved stability of blueberry juice anthocyanins by acidification and refrigeration. *J. Berry Res.* **2016**, *6*, 189–201, doi:10.3233/JBR-160133.

85. Lee, J.; Durst, R.W.; Wrolstad, R.E. Determination of total monomeric anthocyanin pigment content of fruit juices, beverages, natural colorants, and wines by the pH differential method: Collaborative study. *J. AOAC Int.* **2005**, *88*, 1269–1278, doi:10.1093/jaoac/88.5.1269.

86. Gardeli, C.; Varela, K.; Krokida, E.; Mallouchos, A. Investigation of anthocyanins stability from pomegranate juice (*Punica Granatum* L. Cv Ermioni) under a simulated digestion process. *Medicines* **2019**, *6*, 90.

87. Turfan, Ö.; Türkyilmaz, M.; Yemi, O.; Özkan, M. Anthocyanin and colour changes during processing of pomegranate (*Punica granatum* L.; Cv. Hicaznar) juice from sacs and whole fruit. *Food Chem.* **2011**, *129*, 1644–1651, doi:10.1016/j.foodchem.2011.06.024.

88. Sánchez-Moreno, C.; Cao, G.; Ou, B.; Prior, R.L. Anthocyanin and proanthocyanidin content in selected white and red wines. Oxygen radical absorbance capacity comparison with nontraditional wines obtained from highbush blueberry. *J. Agric. Food Chem.* **2003**, *51*, 4889–4896, doi:10.1021/jf030081t.

89. Chaudhary, S.; Devi, P.; Bhardwaj, A.; Jha, U.C.; Sharma, K.D.; Prasad, P.V.V.; Siddique, K.H.M.; Bindumadhava, H.; Kumar, S.; Nayyar, H. Identification and characterization of contrasting genotypes/cultivars for developing heat tolerance in agricultural crops: current status and prospects. *Front. Plant Sci.* **2020**, *11*, doi:10.3389/fpls.2020.587264.

90. Howard, L.R.; Castrodale, C.; Brownmiller, C.; Mauromoustakos, A. Jam processing and storage effects on blueberry polyphenolics and antioxidant capacity. *J. Agric. Food Chem.* **2010**, *58*, 4022–4029, doi:10.1021/jf902850h.

91. Sousa De Brito, E.; De Araújo, M.C.P.; Alves, R.E.; Carkeet, C.; Clevidence, B.A.; Novotny, J.A. Anthocyanins present in selected tropical fruits: Acerola, jambolão, jussara, and guajiru. *J. Agric. Food Chem.* **2007**, *55*, 9389–9394, doi:10.1021/jf0715020.

92. Contessa, C.; Botta, R. Comparison of physicochemical traits of red-fleshed, commercial and ancient apple cultivars. *Hortic. Sci.* **2016**, *43*, 159–166, doi:10.17221/132/2015-HORTSCI.

93. Li, H.; Subbiah, V.; Barrow, C.J.; Dunshea, F.R.; Suleria, H.A.R. Phenolic profiling of five different australian grown apples. *Appl. Sci.* **2021**, *11*, 1–21, doi:10.3390/app11052421.

94. Colak, N.; Torun, H.; Gruz, J.; Strnad, M.; Subrtova, M.; Inceer, H.; Ayaz, F.A. Comparison of phenolics and phenolic acid profiles in conjunction with Oxygen Radical Absorbing Capacity (ORAC) in berries of *Vaccinium arctostaphylos* L. and *V. myrtillus* L. *Polish J. Food Nutr. Sci.* **2016**, *66*, 85–91, doi:10.1515/pjfns-2015-0053.

95. Benvenuti, S.; Brighenti, V.; Pellati, F. High-performance liquid chromatography for the analytical characterization of anthocyanins in *Vaccinium myrtillus* L. (bilberry) fruit and food products. *Anal. Bioanal. Chem.* **2018**, *410*, 3559–3571, doi:10.1007/s00216-018-0915-z.

96. Fan-Chiang, H.-J.; Wrolstad, R.E. Anthocyanin pigment composition of blackberries. *J. Food Sci.* **2005**, *70*, 198–202.

97. Liao, X.; Greenspan, P.; Srivastava, A.; Pegg, R.B. Characterizing the phenolic constituents of U.S. Southeastern blackberry cultivars. *J. Berry Res.* **2020**, *10*, 311–327, doi:10.3233/JBR-190475.

98. Šimerdová, B.; Bobríková, M.; Lhotská, I.; Kaplan, J.; Křenová, A.; Šatínský, D. Evaluation of anthocyanin profiles in various blackcurrant cultivars over a three-year period using a fast HPLC-DAD method. *Foods* **2021**, *10*, doi:10.3390/foods10081745.

99. Çelik, H.; Özgen, M.; Serçe, S.; Kaya, C. Phytochemical accumulation and antioxidant capacity at four maturity stages of cranberry fruit. *Sci. Hortic. (Amsterdam).* **2008**, *117*, 345–348, doi:10.1016/j.scienta.2008.05.005.

100. Ozgen, M.; Scheerens, J.; Reese, R.; Miller, R. Total phenolic, anthocyanin contents and antioxidant capacity of selected elderberry (*Sambucus canadensis* L.) accessions. *Pharmacogn. Mag.* **2010**, *6*, 198–203, doi:10.4103/0973-1296.66936.

101. Duymuş, H.G.; Göger, F.; Başer, K.H.C. In vitro antioxidant properties and anthocyanin compositions of elderberry extracts. *Food Chem.* **2014**, *155*, 112–119, doi:10.1016/j.foodchem.2014.01.028.

102. Zhang, X.; Wang, X.; Liu, L.; Wang, W.; Liu, Y.; Deng, Q.; Zhang, H.; Wang, X.; Xia, H. Evaluation of the comparative morphological and quality in fig (Sichuan, China) with different colors under different ripening stages. *Sci. Hortic. (Amsterdam).* **2020**, *265*, 109256, doi:10.1016/j.scienta.2020.109256.

103. Aljane, F.; Neily, M.H.; Msaddak, A. Phytochemical characteristics and antioxidant activity of several fig (*Ficus Carica* L.) ecotypes. *Ital. J. Food Sci.* **2020**, *32*, 755–768, doi:10.14674/IJFS.1884.

104. Silva, A.B.H.K.; Rupasinghe, H.P.V. Effect of growing location on anthocyanin content and total antioxidant capacity of haskap (*Lonicera caerulea* L.) berry: A preliminary investigation. *Hortic. Sci.* **2021**, *48*, 183–189, doi:10.17221/79/2020-HORTSCI.

105. Khattab, R.; Brooks, M.S.L.; Ghanem, A. Phenolic analyses of haskap berries (*Lonicera caerulea* L.): Spectrophotometry versus high performance liquid chromatography. *Int. J. Food Prop.* **2015**, *19*, 1708–1725, doi:10.1080/10942912.2015.1084316.

106. Fujita, R.; Hayasaka, T.; Jin, S.; Hui, S.P.; Hoshino, Y. Comparison of anthocyanin distribution in berries of Haskap (*Lonicera caerulea* subsp. *edulis* (Turcz. ex. Herder) Hultén), Miyama-uguisu-kagura (*Lonicera gracilipes* Miq.), and their interspecific hybrid using imaging mass spectrometry. *Plant Sci.* **2020**, *300*, 110633, doi:10.1016/j.plantsci.2020.110633.

107. Abidi, W.; Zeballos, J.L.; Granell, A.; Gogorcena, Y. Bioactive compounds , sugar content and volatiles compounds in nectarine (*Prunus persica* (L.) Batsch) fruits. *J. new Sci.* **2015**, 830–835.

108. Tomás-Barberán, F.A.; Gil, M.I.; Cremin, P.; Waterhouse, A.L.; Hess-Pierce, B.; Kader, A.A. HPLC-DAD-ESIMS analysis of phenolic compounds in nectarines, peaches, and plums. *J. Agric. Food Chem.* **2001**, *49*, 4748–4760, doi:10.1021/jf0104681.

109. Bento, C.; Gonçalves, A.C.; Silva, B.; Silva, L.R. Assessing the phenolic profile, antioxidant, antidiabetic and protective effects against oxidative damage in human erythrocytes of peaches from Fundão. *J. Funct. Foods* **2018**, *43*, 224–233, doi:10.1016/j.jff.2018.02.018.

110. Reig, G.; Iglesias, I.; Gatius, F.; Alegre, S. Antioxidant capacity, quality, and anthocyanin and nutrient contents of several peach cultivars [Prunus persica (L.) Batsch] grown in Spain. *J. Agric. Food Chem.* **2013**, *61*, 6344–6357, doi:10.1021/jf401183d.

111. Usenik, V.; Štampar, F.; Veberič, R. Anthocyanins and fruit colour in plums (*Prunus domestica* L.) during ripening. *Food Chem.* **2009**, *114*, 529–534, doi:10.1016/j.foodchem.2008.09.083.

112. Russo, M.; Fanali, C.; Tripodo, G.; Dugo, P.; Muleo, R.; Dugo, L.; Gara, L.; Mondello, L. Analysis of phenolic compounds in different parts of pomegranate (Punica granatum) fruit by HPLC-PDA-ESI/MS and evaluation of their antioxidant activity: application to different Italian varieties. *Anal. Bioanal. Chem.* **2018**, *410*, 3507–3520.

113. Gómez-Caravaca, A.M.; Verardo, V.; Toselli, M.; Segura-Carretero, A.; Fernández-Gutiérrez, A.; Caboni, M.F. Determination of the major phenolic compounds in pomegranate juices by HPLC-DAD-ESI-MS. *J. Agric. Food Chem.* **2013**, *61*, 5328–5337, doi:10.1021/jf400684n.

114. Feng Zhu; Zhaohe Yuan; Xueqing Zhao; Yanlei Yin; Lijuan Feng Composition and contents of anthocyanins in different pomegranate cultivars. *Acta Hortic.* **2015**, 35–41, doi:10.17660/actahortic.2015.1089.3.

115. Laczkó-zöld, E.; Komlósi, R.; Ülkei, T.; Fogarasi, E.; Croitoru, M.; Fülöp, I.; Domokos, E.; Ştefănescu, R.; Varga, E. Extractability of polyphenols from black currant, red currant and gooseberry and their antioxidant activity. *Acta Biol. Hung.* **2018**, *69*, 156–169, doi:10.1556/018.69.2018.2.5.

116. Djordjević, B.; Šavikin, K.; Zdunić, G.; Janković, T.; Vulić, T.; Oparnica, Č.; Radivojević, D. Biochemical properties of red currant varieties in relation to storage. *Plant Foods Hum. Nutr.* **2010**, *65*, 326–332, doi:10.1007/s11130-010-0195-z.

117. Hariram Nile, S.; Hwan Kim, D.; Keum, Y.-S. Determination of anthocyanin content and antioxidant capacity of different grape varieties. *Ciência e Técnica Vitivinícola* **2015**, *30*, 60–68, doi:10.1051/ctv/20153002060.

118. Silva, L.R.; Queiroz, M. Bioactive compounds of red grapes from Dão region (Portugal): Evaluation of phenolic and organic profile. *Asian Pac. J. Trop. Biomed.* **2016**, *6*, doi:10.1016/j.apjtb.2015.12.015.

119. Costa, E.; Cosme, F.; Jordão, A.M.; Mendes-Faia, A. Anthocyanin profile and antioxidant activity from 24 grape varieties cultivated in two Portuguese wine regions. *J. Int. des Sci. la Vigne du Vin* **2014**, *48*, 51–62, doi:10.20870/oeno-one.2014.48.1.1661.

120. Galvis Sánchez, A.C.; Gil-Izquierdo, A.; Gil, M.I. Comparative study of six pear cultivars in terms of their phenolic and vitamin C contents and antioxidant capacity. *J. Sci. Food Agric.* **2003**, *83*, 995–1003, doi:10.1002/jsfa.1436.

121. Dussi, M.C.; Sugar, D.; Wrolstad, R.E. Characterizing and quantifying anthocyanins in red pears and the effect of light quality on fruit color. *Mem. Fac. Agric. Kagoshima Univ.* **1995**, *120*, 785–789.

122. Karaaslan, N.M.; Yaman, M. Anthocyanin profile of strawberry fruit as affected by extraction conditions. *Int. J. Food Prop.* **2018**, *20*, S2313–S2322, doi:10.1080/10942912.2017.1368548.

123. Lopes-Da-Silva, F.; De Pascual-Teresa, S.; Rivas-Gonzalo, J.; Santos-Buelga, C. Identification of anthocyanin pigments in strawberry (cv Camarosa) by LC using DAD and ESI-MS detection. *Eur. Food Res. Technol.* **2002**, *214*, 248–253, doi:10.1007/s00217-001-0434-5.

124. Diep, T.; Pook, C.; Yoo, M. Phenolic and anthocyanin compounds and antioxidant activity of Tamarillo (*Solanum betaceum* Cav.). *Antioxidants* **2020**, *9*, 1–20, doi:10.3390/antiox9020169.

125. Picariello, G.; Ferranti, P.; De Cunzo, F.; Sacco, E.; Volpe, M.G. Polyphenol patterns to trace sweet (*Prunus avium*) and tart (*Prunus cerasus*) varieties in cherry jam. *J. Food Sci. Technol.* **2017**, *54*, 2316–2323, doi:10.1007/s13197-017-2670-0.

126. Wang, H.; Sun, S.; Zhou, Z.; Qiu, Z.; Cui, X. Rapid analysis of anthocyanin and its structural modifications in fresh tomato fruit. *Food Chem.* **2020**, *333*, 127439, doi:10.1016/j.foodchem.2020.127439.

127. Blando, F.; Berland, H.; Maiorano, G.; Durante, M.; Mazzucato, A.; Picarella, M.E.; Nicoletti, I.; Gerardi, C.; Mita, G.; Andersen, Ø.M. Nutraceutical characterization of anthocyanin-rich fruits produced by "Sun Black" tomato line. *Front. Nutr.* **2019**, *6*, 133, doi:10.3389/fnut.2019.00133.

128. Montilla, E.C.; Arzaba, M.R.; Hillebrand, S.; Winterhalter, P. Anthocyanin composition of black carrot (*Daucus carota* ssp. *sativus* var. *atrorubens* Alef.) Cultivars antonina, beta sweet, deep purple, and purple haze. *J. Agric. Food Chem.* **2011**, *59*, 3385–3390, doi:10.1021/jf104724k.

129. Koley, T.K.; Tiwari, S.K.; Sarkar, A.; Nishad, J.; Goswami, A.; Singh, B. Antioxidant potential of Indian eggplant: comparison among white, purple and green genotypes using chemometrics. *Agric. Res.* **2019**, *8*, 9–20, doi:10.1007/s40003-018-0347-1.

130. Kurnianingsih, N.; Ratnawati, R.; Nazwar, T.A.; Ali, M.; Fatchiyah, F. Purple sweet potatoes from East Java of Indonesia revealed the macronutrient, anthocyanin compound and antidepressant activity candidate. *Med. Arch. (Sarajevo, Bosnia Herzegovina)* **2021**, *75*, 94–100, doi:10.5455/medarh.2021.75.94-100.

131. Zhu, Z.; Guan, Q.; Guo, Y.; He, J.; Liu, G.; Li, S.; Barba, F.J.; Jaffrin, M.Y. Green ultrasound-assisted extraction of anthocyanin and phenolic compounds from purple sweet potato using response surface methodology. *Int. Agrophysics* **2016**, *30*, 113–122, doi:10.1515/intag-2015-0066.

132. Zhang, J.; Wang, Z.; Liu, X. Characterization of acylated anthocyanins in red cabbage via comprehensive two-dimensional high performance liquid chromatography and HPLC-MS. *J. Food Process. Preserv.* **2017**, *41*, 1–7, doi:10.1111/jfpp.13129.

133. Ahmadiani, N.; Robbins, R.J.; Collins, T.M.; Giusti, M.M. Anthocyanins contents, profiles, and color characteristics of red cabbage extracts from different cultivars and maturity stages. *J. Agric. Food Chem.* **2014**, *62*, 7524–7531, doi:10.1021/jf501991q.

134. Migliorini, A.A.; Piroski, C.S.; Daniel, T.G.; Cruz, T.M.; Escher, G.B.; Vieira do Carmo, M.A.; Azevedo, L.; Marques, M.B.; Granato, D.; Rosso, N.D. Red chicory (*Cichorium intybus*) extract rich in anthocyanins: chemical stability, antioxidant activity, and antiproliferative activity in vitro. *J. Food Sci.* **2019**, *84*, 990–1001, doi:10.1111/1750-3841.14506.

135. D'Evoli, L.; Lucarini, M.; Lombardi-Boccia, G.; Valentini, M.; Potenza, A.; Ritota, M.; Sequi, P. Anthocyanin profile of two Italian Cichorium intybus L. cultivars. *Acta Hortic.* **2012**, *939*, 337–343, doi:10.17660/ActaHortic.2012.939.44.

136. Zhang, S. lin; Deng, P.; Xu, Y. chao; Lü, S. wu; Wang, J. jun Quantification and analysis of anthocyanin and flavonoids compositions, and antioxidant activities in onions with three different colors. *J. Integr. Agric.* **2016**, *15*, 2175–2181, doi:10.1016/S2095-3119(16)61385-0.

137. González-De-Peredo, A. V.; Vázquez-Espinosa, M.; Espada-Bellido, E.; Ferreiro-González, M.; Carrera, C.; Barbero, G.F.; Palma, M. Extraction of antioxidant compounds from onion bulb (*Allium cepa* L.) using individual and Simultaneous microwave-assisted extraction methods. *Antioxidants* **2022**, *11*, doi:10.3390/antiox11050846.

138. Akhavan, H.; Barzegar, M.; Weidlich, H.; Zimmermann, B.F. Phenolic compounds and antioxidant activity of juices from ten Iranian pomegranate cultivars depend on extraction. *J. Chem.* **2015**, *2015*, 11–14, doi:10.1155/2015/907101.

139. Wrolstad, R.E.; Boyles, M.J. Anthocyanin composition of red raspberry juice: Influences of cultivar, processing, and environmental factors. *J. Food Sci.* **1993**, *58*, 1135–1141.

140. Stoj, A.; Malik, A.; Targonski, Z. Comparative analysis of anthocyanin composition of juices obtained from selected species of berry fruits. *Polish J. Food Nutr. Sci.* **2006**, *15*, 401–407.

141. Kharadze, M.; Japaridze, I.; Kalandia, A.; Vanidze, M. Anthocyanins and antioxidant activity of red wines made from endemic grape varieties. *Ann. Agrar. Sci.* **2018**, *16*, 181–184, doi:10.1016/j.aasci.2018.04.006.

142. Damar, I.; Ekşi, A. Antioxidant capacity and anthocyanin profile of sour cherry (*Prunus cerasus* L.) juice. *Food Chem.* **2012**, *135*, 2910–2914, doi:10.1016/j.foodchem.2012.07.032.

143. Zou, T. Bin; Feng, D.; Song, G.; Li, H.W.; Tang, H.W.; Ling, W.H. The role of sodium-dependent glucose transporter 1 and glucose transporter 2 in the absorption of cyanidin-3-*O*-*β*-glucoside in Caco-2 cells. *Nutrients* **2014**, *6*, 4165–4177, doi:10.3390/nu6104165.

144. Keppler, K.; Humpf, H.U. Metabolism of anthocyanins and their phenolic degradation products by the intestinal microflora. *Bioorganic Med. Chem.* **2005**, *13*, 5195–5205, doi:10.1016/j.bmc.2005.05.003.

145. Talavéra, S.; Felgines, C.; Texier, O.; Besson, C.; Manach, C.; Lamaison, J.L.; Rémésy, C. Anthocyanins are efficiently absorbed from the small intestine in rats. *J. Nutr.* **2004**, *134*, 2275–2279, doi:10.1093/jn/134.9.2275.

146. Kuntz, S.; Rudloff, S.; Asseburg, H.; Borsch, C.; Fröhling, B.; Unger, F.; Dold, S.; Spengler, B.; Römpp, A.; Kunz, C. Uptake and bioavailability of anthocyanins and phenolic acids from grape/blueberry juice and smoothie in vitro and in vivo. *Br. J. Nutr.* **2015**, *113*, 1044–1055, doi:10.1017/S0007114515000161.

147. Bresciani, L.; Martini, D.; Mena, P.; Tassotti, M.; Calani, L.; Brigati, G.; Brighenti, F.; Holasek, S.; Malliga, D.E.; Lamprecht, M.; Rio, D.D. Absorption profile of (poly)phenolic compounds after consumption of three food supplements containing 36 different fruits, vegetables, and berries. *Nutrients* **2017**, *9*, 1–17, doi:10.3390/nu9030194.

148. Felgines, C.; Texier, O.; Besson, C.; Lyan, B.; Lamaison, J.L.; Scalbert, A. Strawberry pelargonidin glycosides are excreted in urine as intact glycosides and glucuronidated pelargonidin derivatives in rats. *Br. J. Nutr.* **2007**, *98*, 1126–1131, doi:10.1017/S0007114507764772.

149. McGhie, T.K.; Ainge, G.D.; Barnett, L.E.; Cooney, J.M.; Jensen, D.J. Anthocyanin glycosides from berry fruit are absorbed and excreted unmetabolized by both humans and rats. *J. Agric. Food Chem.* **2003**, *51*, 4539–4548, doi:10.1021/jf026206w.

150. Kay, C.D.; Mazza, G.; Holub, B.J.; Wang, J. Anthocyanin metabolites in human urine and serum. *Br. J. Nutr.* **2004**, *91*, 933–942, doi:10.1079/bjn20041126.

151. Bub, A.; Watzl, B.; Heeb, D.; Rechkemmer, G.; Briviba, K. Malvidin-3-glucoside bioavailability in humans after ingestion of red wine, dealcoholized red wine and red grape juice. *Eur. J. Nutr.* **2001**, *40*, 113–120.

152. Carkeet, C.; Clevidence, B.A.; Novotny, J.A. Anthocyanin excretion by humans increases linearly with increasing strawberry dose. *J. Nutr.* **2008**, *138*, 897–902, doi:10.1093/jn/138.5.897.

153. Kamonpatana, K.; Giusti, M.M.; Chitchumroonchokchai, C.; Morenocruz, M.; Riedl, K.M.; Kumar, P.; Failla, M.L. Susceptibility of anthocyanins to *ex vivo* degradation in human saliva. *Food Chem.* **2012**, *135*, 738–747, doi:10.1016/j.foodchem.2012.04.110.

154. Ludwig, I.A.; Mena, P.; Calani, L.; Borges, G.; Pereira-Caro, G.; Bresciani, L.; Del Rio, D.; Lean, M.E.J.; Crozier, A. New insights into the bioavailability of red raspberry anthocyanins and ellagitannins. *Free Radic. Biol. Med.* **2015**, *89*, 758–769, doi:10.1016/j.freeradbiomed.2015.10.400.

155. Mazza, G.; Kay, C.D.; Cottrell, T.; Holub, B.J. Absorption of anthocyanins from blueberries and serum antioxidant status in human subjects. *J. Agric. Food Chem.* **2002**, *50*, 7731–7737, doi:10.1021/jf020690l.

156. Krga, I.; Milenkovic, D. Anthocyanins: From sources and bioavailability to cardiovascular-health benefits and molecular mechanisms of action. *J. Agric. Food Chem.* **2019**, *67*, 1771–1783, doi:10.1021/acs.jafc.8b06737.

157. Agulló, V.; Villaño, D.; García-Viguera, C.; Domínguez-Perles, R. Anthocyanin metabolites in human urine after the intake of new functional beverages. *Molecules* **2020**, *25*, doi:10.3390/molecules25020371.

158. Chen, J.; Shu, Y.; Chen, Y.; Ge, Z.; Zhang, C.; Cao, J.; Li, X.; Wang, Y.; Sun, C. Evaluation of antioxidant capacity and gut microbiota modulatory effects of different kinds of berries. *Antioxidants* **2022**, *11*, 1020, doi:10.3390/antiox11051020.

159. Bulatao, R.M.; Samin, J.P.A.; Salazar, J.R.; Monserate, J.J. Encapsulation of anthocyanins from black rice (*Oryza sativa* L.) bran extract using chitosan-alginate nanoparticles. *J. Food Res.* **2017**, *6*, 40, doi:10.5539/jfr.v6n3p40.

160. Cui, H.; Si, X.; Tian, J.; Lang, Y.; Gao, N.; Tan, H.; Bian, Y.; Zang, Z.; Jiang, Q.; Bao, Y.; Li, B. Anthocyanins-loaded nanocomplexes comprising casein and carboxymethyl cellulose: stability, antioxidant capacity, and bioaccessibility. *Food Hydrocoll.* **2022**, *122*, doi:10.1016/j.foodhyd.2021.107073.

161. Ravanfar, R.; Tamaddon, A.M.; Niakousari, M.; Moein, M.R. Preservation of anthocyanins in solid lipid nanoparticles: Optimization of a microemulsion dilution method using the Placket-Burman and Box-Behnken designs. *Food Chem.* **2016**, *199*, 573–580, doi:10.1016/j.foodchem.2015.12.061.

162. Yao, L.; Xu, J.; Zhang, L.; Liu, L.; Zhang, L. Nanoencapsulation of anthocyanin by an amphiphilic peptide for stability enhancement. *Food Hydrocoll.* **2021**, *118*, 106741, doi:10.1016/j.foodhyd.2021.106741.

163. Priprem, A.; Damrongrungruang, T.; Limsitthichaikoon, S.; Khampaenjiraroch, B.; Nukulkit, C.; Thapphasaraphong, S.; Limphirat, W. Topical niosome gel containing an anthocyanin complex: a potential oral wound healing in rats. *AAPS PharmSciTech* **2018**, *19*, 1681–1692, doi:10.1208/s12249-018-0966-7.

164. Ge, J.; Yue, P.; Chi, J.; Liang, J.; Gao, X. Formation and stability of anthocyanins-loaded nanocomplexes prepared with chitosan hydrochloride and carboxymethyl chitosan. *Food Hydrocoll.* **2018**, *74*, 23–31, doi:10.1016/j.foodhyd.2017.07.029.

165. Nazareth, M.S.; Shreelakshmi, S. V.; Rao, P.J.; Shetty, N.P. Micro and nanoemulsions of *Carissa spinarum* fruit polyphenols, enhances anthocyanin stability and anti-quorum sensing activity: Comparison of degradation kinetics. *Food Chem.* **2021**, *359*, 129876, doi:10.1016/j.foodchem.2021.129876.

166. Xu, C.; Wang, Y.; Yu, H.; Tian, H.; Chen, X. Multifunctional theranostic nanoparticles derived from fruit-extracted anthocyanins with dynamic disassembly and elimination abilities. *ACS Nano* **2018**, *12*, 8255–8265, doi:10.1021/acsnano.8b03525.

167. Wu, H.; Wang, M.; Zhu, J.; Li, Z.; Wang, W.; Gu, L.; Shen, F.; Yang, T. Mesoporous nanoparticles for diagnosis and treatment of liver cancer in the era of precise medicine. *Pharmaceutics* **2022**, *14*, 1760.

168. Bahlool, A.Z.; Fattah, S.; Sullivan, A.O.; Cavanagh, B.; Macloughlin, R.; Keane, J.; Sullivan, M.P.O.; Cryan, S.A. Development of inhalable ATRA-Loaded PLGA nanoparticles as host-directed immunotherapy against tuberculosis. *Pharmaceutics* **2022**, *14*, 1745.

169. Suner, S.S.; Sahiner, M.; Ayyala, R.S.; Sahiner, N. Degradable and non-degradable chondroitin sulfate particles with the controlled antibiotic release for bacterial infections. *Pharmaceutics* **2022**, *14*, 1739.

170. Wang, Q.; Ma, R.; Liu, P.; Cheng, G.; Yang, Q.; Chen, X.; Wu, Z.; Yuan, D.; Chen, T. Efficient sustained-release nanoparticle delivery system protects nigral neurons in a toxin model of Parkinson's disease. *Pharmaceutics* **2022**, *14*, 1732.

171. Saifullah, M.; Shishir, M.R.I.; Ferdowsi, R.; Tanver Rahman, M.R.; Van Vuong, Q. Micro and nano encapsulation, retention and controlled release of flavor and aroma compounds: A critical review. *Trends Food Sci. Technol.* **2019**, *86*, 230–251, doi:10.1016/j.tifs.2019.02.030.

172. Chen, L.; Lin, X.; Xu, X.; Chen, Y.; Li, K.; Fan, X.; Pang, J.; Teng, H. Self-nano-emulsifying formulation of Sonchus oleraceus Linn for improved stability: Implications for phenolics degradation under in vitro gastro-intestinal digestion: Food grade drug delivery system for crude extract but not single compound. *J. Funct. Foods* **2019**, *53*, 28–35, doi:10.1016/j.jff.2018.12.009.

173. Ohta, S.; Kikuchi, E.; Ishijima, A.; Azuma, T.; Sakuma, I.; Ito, T. Investigating the optimum size of nanoparticles for their delivery into the brain assisted by focused ultrasound-induced blood–brain barrier opening. *Sci. Rep.* **2020**, *10*, 1–13, doi:10.1038/s41598-020-75253-9.

174. Munagala, R.; Aqil, F.; Jeyabalan, J.; Agrawal, A.K.; Mudd, A.M.; Kyakulaga, A.H.; Singh, I.P.; Vadhanam, M. V.; Gupta, R.C. Exosomal formulation of anthocyanidins against multiple cancer types. *Cancer Lett.* **2017**, *393*, 94–102, doi:10.1016/j.canlet.2017.02.004.

175. Chatterjee, N.S.; Dara, P.K.; Perumcherry Raman, S.; Vijayan, D.K.; Sadasivam, J.; Mathew, S.; Ravishankar, C.N.; Anandan, R. Nanoencapsulation in low-molecular-weight chitosan improves in vivo antioxidant potential of black carrot anthocyanin. *J. Sci. Food Agric.* **2021**, *101*, 5264–5271, doi:10.1002/jsfa.11175.

176. Karim, N.; Shishir, M.R.I.; Li, Y.; Zineb, O.Y.; Mo, J.; Tangpong, J.; Chen, W. Pelargonidin-3-*O*-glucoside encapsulated pectin-chitosan-nanoliposomes recovers palmitic acid-induced hepatocytes injury. *Antioxidants* **2022**, *11*, doi:10.3390/antiox11040623.

177. Pateiro, M.; Gómez, B.; Munekata, P.E.S.; Barba, F.J.; Putnik, P.; Kovačević, D.B.; Lorenzo, J.M. Nanoencapsulation of promising bioactive compounds to improve their absorption, stability, functionality and the appearance of the final food products. *Molecules* **2021**, *26*, doi:10.3390/molecules26061547.

178. Homayoonfal, M.; Mousavi, S.M.; Kiani, H.; Askari, G.; Desobry, S.; Arab-Tehrany, E. Encapsulation of berberis vulgaris anthocyanins into nanoliposome composed of rapeseed lecithin: A comprehensive study on physicochemical characteristics and biocompatibility. *Foods* **2021**, *10*, doi:10.3390/foods10030492.

179. Wang, M.; Li, L.; Wan, M.; Lin, Y.; Tong, Y.; Cui, Y.; Deng, H.; Tan, C.; Kong, Y.; Meng, X. Preparing, optimising, and evaluating chitosan nanocapsules to improve the stability of anthocyanins from Aronia melanocarpa. *RSC Adv.* **2020**, *11*, 210–218, doi:10.1039/d0ra08162k.

180. Ge, J.; Yue, X.; Wang, S.; Chi, J.; Liang, J.; Sun, Y.; Gao, X.; Yue, P. Nanocomplexes composed of chitosan derivatives and β-Lactoglobulin as a carrier for anthocyanins: Preparation, stability and bioavailability in vitro. *Food Res. Int.* **2019**, *116*, 336–345, doi:10.1016/j.foodres.2018.08.045.

181. Osvaldt Rosales, T.K.; Pessoa da Silva, M.; Lourenço, F.R.; Aymoto Hassimotto, N.M.; Fabi, J.P. Nanoencapsulation of anthocyanins from blackberry (*Rubus* spp.) through pectin and lysozyme self-assembling. *Food Hydrocoll.* **2021**, *114*, doi:10.1016/j.foodhyd.2020.106563.

182. Chotiko, A.; Sathivel, S. Releasing characteristics of anthocyanins extract in pectin–whey protein complex microcapsules coated with zein. *J. Food Sci. Technol.* **2017**, *54*, 2059–2066, doi:10.1007/s13197-017-2643-3.

183. Zhao, L.; Temelli, F.; Chen, L. Encapsulation of anthocyanin in liposomes using supercritical carbon dioxide: Effects of anthocyanin and sterol concentrations. *J. Funct. Foods* **2017**, *34*, 159–167, doi:10.1016/j.jff.2017.04.021.

184. Thibado, S.; Thornthwaite, J.; Ballard, T.; Goodman, B. Anticancer effects of bilberry anthocyanins compared with NutraNanoSphere encapsulated bilberry anthocyanins. *Mol. Clin. Oncol.* **2018**, *8*, 330–335, doi:10.3892/mco.2017.1520.

185. Chi, J.; Ge, J.; Yue, X.; Liang, J.; Sun, Y.; Gao, X.; Yue, P. Preparation of nanoliposomal carriers to improve the stability of anthocyanins. *Lwt* **2019**, *109*, 101–107, doi:10.1016/j.lwt.2019.03.070.

186. Peanparkdee, M.; Borompichaichartkul, C.; Iwamoto, S. Bioaccessibility and antioxidant activity of phenolic acids, flavonoids, and anthocyanins of encapsulated Thai rice bran extracts during *in vitro* gastrointestinal digestion. *Food Chem.* **2021**, *361*, 130161, doi:10.1016/j.foodchem.2021.130161.

187. Barretto, F.J. de F.P.; Clemente, H.A.; Santana, A.L.B.D.; Vasconcelo, M.A. da S. Stability of encapsulated and non-encapsulated anthocyanin in yogurt produced with natural dye obtained from *Solanum melongena* L. bark. *Rev. Bras. Frutic.* **2020**, *42*, 1–13, doi:10.1590/0100-29452020137.

188. Qin, X.; Yuan, D.; Wang, Q.; Hu, Z.; Wu, Y.; Cai, J.; Huang, Q.; Li, S.; Liu, G. Maillard-reacted whey protein isolates enhance yhermal stability of anthocyanins over a wide pH range. *J. Agric. Food Chem.* **2018**, *66*, 9556–9564, doi:10.1021/acs.jafc.8b03125.

189. Zhang, T.; Lv, C.; Chen, L.; Bai, G.; Zhao, G.; Xu, C. Encapsulation of anthocyanin molecules within a ferritin nanocage increases their stability and cell uptake efficiency. *Food Res. Int.* **2014**, *62*, 183–192, doi:10.1016/j.foodres.2014.02.041.

190. Dupeyrón, D.; Kawakami, M.; Rieumont, J.; Carvalho, J.C. Synthesis and characterization of anthocyanins-loaded nanoparticles formulation and characterization of anthocyanins-loaded nanoparticles. *Curr. Drug Deliv.* **2017**, *14*, doi:10.2174/1567201813666160915021.

191. Buljeta, I.; Pichler, A.; Ivić, I.; Šimunović, J.; Kopjar, M. Encapsulation of fruit flavor compounds through interaction with polysaccharides. *Molecules* **2021**, *26*, 1–28, doi:10.3390/molecules26144207.

192. Mendes, D.; Valentão, P.; Oliveira, M.M.; Andrade, P.; Videira, R.A. A nanophytosomes formulation based on elderberry anthocyanins and Codium lipids to mitigate mitochondrial dysfunctions. *Biomed. Pharmacother.* **2021**, *143*, doi:10.1016/j.biopha.2021.112157.

193. Tan, C.; Arshadi, M.; Lee, M.C.; Godec, M.; Azizi, M.; Yan, B.; Eskandarloo, H.; Deisenroth, T.W.; Darji, R.H.; Pho, T.V.; Abbaspourrad, A. A robust aqueous core-shell-shell coconut-like nanostructure for stimuli-responsive delivery of hydrophilic cargo. *ACS Nano* **2019**, *13*, 9016–9027, doi:10.1021/acsnano.9b03049.

194. Yesil-Celiktas, O.; Pala, C.; Cetin-Uyanikgil, E.O.; Sevimli-Gur, C. Synthesis of silica-PAMAM dendrimer nanoparticles as promising carriers in Neuro blastoma cells. *Anal. Biochem.* **2017**, *519*, 1–7, doi:10.1016/j.ab.2016.12.004.

195. Duarte, H.A. Molecular simulation of nanosized tubular clay minerals. In *Developments in Clay Science*; Elsevier Ltd., 2016; Vol. 7, pp. 331–359 ISBN 9780081002933.

196. Samadder, A.; Tarafdar, D.; Abraham, S.K.; Ghosh, K.; Khuda-Bukhsh, A.R. Nano-pelargonidin protects hyperglycemic-induced L6 cells against mitochondrial dysfunction. *Planta Med.* **2017**, *83*, 468–475, doi:10.1055/s-0043-100017.

197. Samadder, A.; Tarafdar, D.; Das, R.; Khuda-Bukhsh, A.R.; Abraham, S.K. Efficacy of nanoencapsulated pelargonidin in ameliorating pesticide toxicity in fish and L6 cells: Modulation of oxidative stress and signalling cascade. *Sci. Total Environ.* **2019**, *671*, 466–473, doi:10.1016/j.scitotenv.2019.03.381.

198. Samadder, A.; Abraham, S.K.; Khuda-Bukhsh, A.R. Nanopharmaceutical approach using pelargonidin towards enhancement of efficacy for prevention of alloxan-induced DNA damage in L6 cells via activation of PARP and p53. *Environ. Toxicol. Pharmacol.* **2016**, *43*, 27–37, doi:10.1016/j.etap.2016.02.010.

199. Amin, F.U.; Shah, S.A.; Badshah, H.; Khan, M.; Kim, M.O. Anthocyanins encapsulated by PLGA@PEG nanoparticles potentially improved its free radical scavenging capabilities via p38/JNK pathway against Aβ$_{1-42}$-induced oxidative stress. *J. Nanobiotechnology* **2017**, *15*, 1–16, doi:10.1186/s12951-016-0227-4.

200. Barkallah, M.; Nzoughet-Kouassi, J.; Simard, G.; Thoulouze, L.; Marze, S.; Ropers, M.H.; Andriantsitohaina, R. Enhancement of the anti-angiogenic effects of delphinidin when encapsulated within small extracellular vesicles. *Nutrients* **2021**, *13*, doi:10.3390/nu13124378.

201. Aqil, F.; Jeyabalan, J.; Agrawal, A.K.; Kyakulaga, A.H.; Munagala, R.; Parker, L.; Gupta, R.C. Exosomal delivery of berry anthocyanidins for the management of ovarian cancer. *Food Funct.* **2017**, *8*, 4100–4107, doi:10.1039/c7fo00882a.

202. Mudd, A.M.; Gu, T.; Munagala, R.; Jeyabalan, J.; Egilmez, N.K.; Gupta, R.C. Chemoprevention of colorectal cancer by anthocyanidins and mitigation of metabolic shifts induced by dysbiosis of the gut microbiome. *Cancer Prev. Res.* **2020**, *13*, 41–52, doi:10.1158/1940-6207.CAPR-19-0362.Chemoprevention.

203. Fidan-Yardimci, M.; Akay, S.; Sharifi, F.; Sevimli-Gur, C.; Ongen, G.; Yesil-Celiktas, O. A novel niosome formulation for encapsulation of anthocyanins and modelling intestinal transport. *Food Chem.* **2019**, *293*, 57–65, doi:10.1016/j.foodchem.2019.04.086.

204. Kim, M.J.; Rehman, S.U.; Amin, F.U.; Kim, M.O. Enhanced neuroprotection of anthocyanin-loaded PEG-gold nanoparticles against Aβ$_{1-42}$-induced neuroinflammation and neurodegeneration via the NF-KB /JNK/GSK3β signaling pathway. *Nanomedicine Nanotechnology, Biol. Med.* **2017**, *13*, 2533–2544, doi:10.1016/j.nano.2017.06.022.

205. Zhang, J.; Liang, X.; Li, X.; Guan, Z.; Liao, Z.; Luo, Y.; Luo, Y. Ocular delivery of cyanidin-3-glycoside in liposomes and its prevention of selenite-induced oxidative stress. *Drug Dev. Ind. Pharm.* **2016**, *42*, 546–553, doi:10.3109/03639045.2015.1088867.

206. Jeong, D.; Bae, B.C.; Park, S.J.; Na, K. Reactive oxygen species responsive drug releasing nanoparticle based on chondroitin sulfate-anthocyanin nanocomplex for efficient tumor therapy. *J. Control. Release* **2016**, *222*, 78–85, doi:10.1016/j.jconrel.2015.12.009.

207. Liang, T.; Zhang, Z.; Jing, P. Black rice anthocyanins embedded in self-assembled chitosan/chondroitin sulfate nanoparticles enhance apoptosis in HCT-116 cells. *Food Chem.* **2019**, *301*, 125280, doi:10.1016/j.foodchem.2019.125280.

208. Xiong, Y.; Yang, G.; Zhou, H.; Li, W.; Sun, J.; Tao, T.; Li, J. A ROS-responsive self-assembly driven by multiple intermolecular interaction enhances tumor-targeted chemotherapy. *J. Pharm. Sci.* **2021**, *110*, 1668–1675, doi:10.1016/j.xphs.2020.09.046.

209. Patra, J.K.; Das, G.; Fraceto, L.F.; Campos, E.V.R.; Rodriguez-Torres, M.D.P.; Acosta-Torres, L.S.; Diaz-Torres, L.A.; Grillo, R.; Swamy, M.K.; Sharma, S.; Habtemariam, S.; Shin, H.S. Nano based drug delivery systems: Recent developments and future prospects. *J. Nanobiotechnology* **2018**, *16*, 1–33, doi:10.1186/s12951-018-0392-8.

210. Liu, Z.; Hu, Y.; Li, X.; Mei, Z.; Wu, S.; He, Y.; Jiang, X.; Sun, J.; Xiao, J.; Deng, L.; Bai, W. Nanoencapsulation of cyanidin-3-*O*-glucoside enhances protection against UVB-induced epidermal damage through regulation of p53-mediated apoptosis in mice. *J. Agric. Food Chem.* **2018**, *66*, 5359–5367, doi:10.1021/acs.jafc.8b01002.

211. Ali, T.; Kim, M.J.; Rehman, S.U.; Ahmad, A.; Kim, M.O. Anthocyanin-loaded PEG-gold nanoparticles enhanced the neuroprotection of anthocyanins in an $A\beta_{1-42}$ mouse model of Alzheimer's disease. *Mol. Neurobiol.* **2017**, *54*, 6490–6506, doi:10.1007/s12035-016-0136-4.