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COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

Acylated anthocyanins: A review on their bioavailability and effects on postprandial carbohydrate metabolism and inflammation

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Abstract

Anthocyanins, the natural red and purple colorants of berries, fruits, vegetables, and tubers, improve carbohydrate metabolism and decrease the risk factors of metabolic disorders, but their industrial use is limited by their chemical instability. Acylation of the glycosyl moieties of anthocyanins, however, changes the chemical properties of anthocyanins and provides enhanced stability. Thus, acylated anthocyanins are more usable as natural colorants and bioactive components of innovative functional foods. Acylated anthocyanins are common in pigmented vegetables and tubers, the consumption of which has the potential to increase the intake of health-promoting anthocyanins as part of the daily diet. For the first time, this review presents the current findings on bioavailability, absorption, metabolism, and health effects of acylated anthocyanins with comparison to more extensively investigated nonacylated anthocyanins. The structural differences between nonacylated and acylated anthocyanins lead to enhanced color stability, altered absorption, bioavailability, *in vivo* stability, and colonic degradation. The impact of phenolic metabolites and their potential health effects regardless of the low bioavailability of the parent anthocyanins as such is discussed. Here, purple-fleshed potatoes are presented as a globally available, eco-friendly model food rich in acylated anthocyanins, which further highlights the industrial possibilities and nutritional relevance of acylated anthocyanins. This work supports the academic community and industry in food research and development by reviewing the current literature and highlighting gaps of knowledge.

KEYWORDS
acylated anthocyanins, bioavailability, inflammation, nutrition, phenolics, pigments, postprandial carbohydrate metabolism

Nomenclature: Akt, protein kinase B; AMPK, adenosine monophosphate activated protein kinase; CAT, catalase; C_{max}, maximum concentration; GLUT, glucose transporter; GPx, glutathione peroxidase; GR, glutathione reductase; GST, glutathione-S-transferase; HbA1c, glycated hemoglobin; HFD, high-fat diet; iAUC, incremental area under the curve; IL, interleukin; ipGTT, intraperitoneal glucose tolerance test; ipITT, intraperitoneal insulin tolerance test; IRS-1, insulin receptor substrate 1; OGTT, oral glucose tolerance test; PI3K, phosphoinositide 3 kinase; SGLT1, sodium-glucose cotransporter 1; SOD, superoxide dismutase; t_{max}, time at maximum concentration

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1 | INTRODUCTION

Postprandial state is the combination of metabolic processes of nutrient digestion and absorption that follows after the intake of food (Meessen et al., 2019). It typically covers most of the day as cumulative periods of 4–6 h (Monnier, 2000). Imbalanced food intake impairs the postprandial metabolism leading to oxidative stress, inflammation, and in the long-term, disorders, such as type II diabetes and metabolic syndrome (Meessen et al., 2019; Ruiz-Núñez et al., 2013). Repetitive, oscillating high blood glucose peaks are especially detrimental (Ceriello et al., 2008); thus, healthy dietary choices are essential for preventing metabolic disorders together with other lifestyle changes (Ford & Mokdad, 2001; Hu et al., 2001; Tuomilehto et al., 2001).

Emerging research on the plant-based red and purple polyphenolic pigments, the anthocyanins, has given evidence of their health benefits. Epidemiological studies show that the intake of anthocyanin-rich foods, such as berries and fruits, is anti-inflammatory (Cassidy et al., 2015; Jennings et al., 2014), improves insulin resistance (Jennings et al., 2014), and reduces the risk of type II diabetes (Mursu et al., 2014; Wedick et al., 2012). Clinical trials and mechanistic studies suggest beneficial effects on carbohydrate metabolism (Castro-Acosta, Lenihan-Geels, et al., 2016; Coe & Ryan, 2016; Gowd et al., 2017; Guo & Ling, 2015; Guo et al., 2016; Hanhineva et al., 2010; Pojer et al., 2013; Williamson, 2017). Anthocyanins are structurally versatile, differing in the number and position of hydroxy, methoxy, glycosyl, and acyl substituents, which affect their physico-chemical properties, absorption, and metabolism. The health effects, compelling hues, and naturalness of anthocyanins encourage their use in food products as bioactive compounds and natural colorants, but their industrial usage is often limited by their chemical instability.

Acylation of glycosyl moieties of anthocyanins changes their chemical properties, providing increased structural stabilization (Cevallos-Casals & Cisneros-Zevallos, 2004; Zhao et al., 2017) and low visual detection threshold (Stintzing et al., 2002). In nature, acylated anthocyanins are widely found in common edible pigmented vegetables and tubers, and in minor amounts in some berries and fruits (Andersen & Jordheim, 2010; Giusti & Wrolstad, 2003). Consumption of pigmented vegetables and tubers is an affordable way to increase the daily intake of health-promoting anthocyanins. Especially, pigmented potatoes provide a promising edible source of acylated anthocyanins, as the common potato *Solanum tuberosum* L. is already globally cultivated and consumed nongrain staple crop (Spooner et al., 2014). Potatoes have also low ecological burden (Hess et al., 2016) and excellent nutritive value being rich in energy, carbohydrates, potassium, vitamin C and B6, but low in fat (Burlingame et al., 2009). Currently, the estimates for daily anthocyanin intake vary between 6 and 65 mg (Drossard et al., 2013; Murphy et al., 2019; Sebastian et al., 2015; Zamora-Ros et al., 2011), mainly from red wine, fruits, and berries (Igwe et al., 2019; Ovaskainen et al., 2008; Zamora-Ros et al., 2011).

Despite the potential health effects of anthocyanins and the desired structural stability provided by their acylation, the effects of acylation on the absorption, metabolism, and health effects of anthocyanins have not been comprehensively reviewed. For the first time, this review summarizes the scientific research of the health effects of acylated anthocyanins and their natural food sources when possible. Future prospects and gaps in the current knowledge are discussed to provide the full picture of the topic and to highlight both the potential and complexity of the research field. Purple-fleshed potatoes are discussed as a model food due to their high potential as a staple crop and the most potent food source of acylated anthocyanins.

2 | OVERVIEW OF STRUCTURAL CHARACTERISTICS

Anthocyanins consist of a C6-C3-C6 ring system of two hydroxysubstituted benzenes (A- and B-rings) linked by a heterocyclic ring (C-ring), forming a π-conjugated 2-phenylbenzopyrylium cation (flavylium cation) with chromophore properties. The carbons 4′, 3, 5, and 7 are hydroxylated to form the anthocyanin aglycone (anthocyanidin); the hydroxy- and methoxysubstituents in carbons 3′ and 5′ determine its name. The common six anthocyanidins found in edible plants are cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin (Andersen & Jordheim, 2010; Clifford, 2000; Kong et al., 2003; Wallace & Giusti, 2015). As aglycones are unstable, anthocyanins are almost exclusively linked to a sugar moiety via an *O*-glycosidic bond of the hydroxy group of C-3 to form 3-*O*-glycosides (Mazza & Brouillard, 1987). In edible plants, the common sugars linked to anthocyanins are glucose and rhamnose, but also other hexoses, such as galactose, other pentoses, such as xylose and arabinose, and disaccharides, such as rutinose and sambubiose, are found. The carbons C-5, C-7, C-3′, and C-5′ may carry an additional sugar moiety to form an anthocyanin diglucoside (de Pascual-Teresa & Sanchez-Ballesta, 2007).

The sugar moieties of acylated anthocyanins, usually attached to the hydroxyl group in C-3 and C-5 of the aglycone, have a covalent ester linkage to one or more aliphatic or aromatic acids (Harborne & Williams, 1998). The acyl groups present in acylated anthocyanins of edible foods include aliphatic acids, for example, acetic, malonic, oxalic

and succinic acids, and aromatic acids, for example, caffeic, coumaric, ferulic, hydroxybenzoic, and sinapic acids. The acyl group is added to the glycosyl moiety in post-biosynthetic processes via cytoplasmic or vacuolar acyltansferases (Sasaki et al., 2014). The effect of acyl groups on the chemistry of anthocyanins has been extensively reviewed in detail elsewhere (Dangles & Fenger, 2018; Trouillas et al., 2016; Yoshida et al., 2009; Zhao et al., 2017). Shortly, the acylation affects the chemical properties of anthocyanins as the structural size is increased, polarity affected depending on the acyl group, the spatial organization changed, and chemical reactivity decreased. The effect on stability is further discussed in Section 5.1.

Considering different varieties of pigmented potatoes as an example, they contain all six of the aforementioned anthocyanidins (Andersen et al., 1991; Eichhorn & Winterhalter, 2005; Fossen & Andersen, 2000; Fossen et al., 2003; Giusti et al., 2014; Harborne, 1960; Hillebrand et al., 2009; Howard et al., 1970; Ieri et al., 2011; Mori et al., 2010; Mulinacci et al., 2008; Naito et al., 1998; Pillai, 2013; Rodriguez-Saona et al., 1998). The major anthocyanidins of purple varieties are methoxysubstituted petunidin, peonidin, and malvidin (Andersen et al., 1991; Eichhorn & Winterhalter, 2005; Fossen & Andersen, 2000; Fossen et al., 2003; Hillebrand et al., 2009), whereas pelargonidin dominates in the red varieties (Eichhorn & Winterhalter, 2005; Mori et al., 2010; Naito et al., 1998; Rodriguez-Saona et al., 1998). The sugar moieties linked to the anthocyanidin are a glucose in C-5 (5-*O*-glucose) and a rutinose in C-3 (3-*O*-rutinose) (Andersen et al., 1991; Fossen & Andersen, 2000; Fossen et al., 2003; Hillebrand et al., 2009; Naito et al., 1998). An aromatic hydroxycinnamic acid (*p*-coumaric, caffeic, or ferulic acid) is linked to the rutinosyl (Andersen et al., 1991; Fossen & Andersen, 2000; Fossen et al., 2003; Hillebrand et al., 2009; Mori et al., 2010). As an example, petanin (petunidin 3-*O*-[6-*O*-(4-*O*-*E*-*p*-coumaroyl-*O*-*α*-L-rhamnopyranosyl)-*β*-D-glucopyranoside]-5-*O*-*β*-D-glucopyranoside), which is a common acylated anthocyanin in the flesh and peel of purple potatoes (Ieri et al., 2011), is shown in Figure 1 (Andersen et al., 1991; Fossen et al., 2003; Fossen & Andersen, 2000).

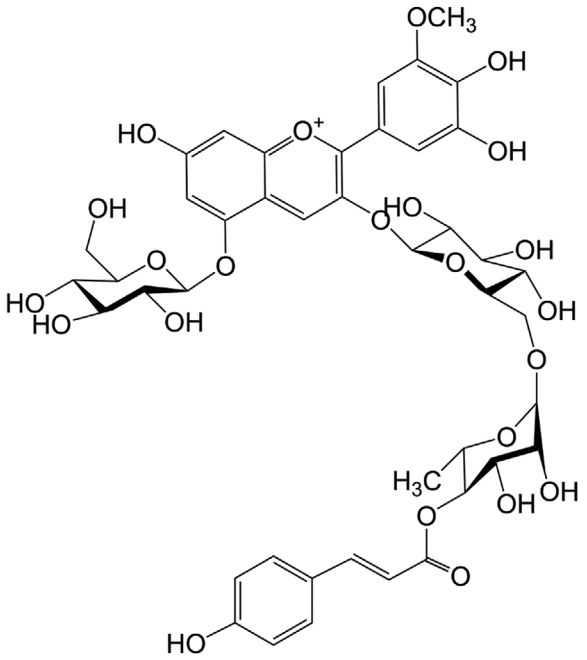


FIGURE 1 The structure of the common acylated anthocyanin found in purple potatoes, petanin. Adapted from Fossen et al. (2003)

3 | FOOD SOURCES

A number of structurally different acylated anthocyanins are found in foods, such as fruits, berries, vegetables, and tubers; rich sources include, for example, purple sweet potato, red radish, purple carrot, and red cabbage (Giusti & Wrolstad, 2003). The pigmented members of the *Solanaceae* family, potatoes, peppers, tomatoes, and eggplants, contain similar type of acylated anthocyanins with the structure of anthocyanidin-3-hydroxycinnamoyl-rutinoside-5-glucoside with delphinidin as the major anthocyanidin apart from pigmented potatoes (Azuma et al., 2008; Butelli et al., 2008; Liu et al., 2018; Sadilova et al., 2006). Depending on the plant, the proportion of acylated anthocyanins of the total anthocyanins vary from below 1% to near 100% (Cebadera-Miranda et al., 2019; Charron et al., 2007; Cheng et al., 2014; Kidøy et al., 1997; Kurilich et al., 2005; Lao & Giusti, 2016; Moreno et al., 2010; Stalmach et al., 2011; Wu & Prior, 2005; Xu et al., 2015) (Table 1). No berry is known to contain acylated anthocyanins as the major anthocyanin type (Jordheim et al., 2007).

The pigmented potato varieties have distinguishable morphological traits due to the differences in genetics giving them a pigmented phenotype in the tuber flesh, skin, and flower (van Eck, 2007). Depending on the variety, the flesh of the pigmented tubers may be partially or totally pigmented with light or dark red or purple, or even white/yellow, whereas the skin is pigmented (Hejtmánková et al., 2013; Ieri et al., 2011; Jansen & Flamme, 2006; Oertel et al., 2017; Reyes et al., 2004). The content of anthocyanins in pigmented potatoes is variety specific (Burlingame et al., 2009; Lachman et al., 2009; Mori et al., 2010), typically ranging between 0.7 and 74.3 mg /100 g fresh weight (Lachman et al., 2009), the average being 41.3 mg/100 g fresh weight (Burlingame et al., 2009; Giusti & Wrolstad, 2003; Reyes & Cisneros-Zevallos, 2007). The amount of anthocyanins is affected by several

TABLE 1 Acylated anthocyanins found in edible berries, fruits, and vegetables

	Types of acylated anthocyanins	Acyl groups	Major acylated anthocyanins	Proportion (%)	References
Berries					
Blackberry	Cy-3-(3′′/6′′-acyl-glu)	Mal	Cy-3-(6′′-mal-glu)	3	Wu et al. (2006)
Blueberry	Cy/dp/mv/pn/pt-3-(6′′-acyl)-glu/gal	Ace, mal	Mv-3-(6′′-ace)-glu	4–13	Wu et al. (2006); Wu and Prior (2005)
Grape (*Vitis labrusca* 'Concord')	Cy/dp/mv/pn/pt-3-(6′′-acyl-(di)glu)	Ace, cou	Dp-3-cou-5-diglu, pt-3-cou-5-diglu	38	Stalmach et al. (2011)
Gooseberry (*Ribes grossularia* L.)	Cy-3-(6′′-acyl-glu)	Caf, cou	Cy-3-(6′′-cou-glu)	14–58	Jordheim et al. (2007)
Jostaberry (*Ribes* x *nidigrolaria*	Cy-3-(6′′-acyl-glu)	Caf, cou	Cy-3-(6′′-cou-glu)	4–7	Jordheim et al. (2007)
Red flowering currant (*Ribes sanguineum*)	Cy-3-(6′′-acyl-glu)	Cou	Cy-3-(6′′-cou-glu)	1	Jordheim et al. (2007)
Fruits					
Black plum	Cy-3-acyl-glu	Mal, ace	Cy-3-(6′′-ace)-glu	<1	Wu et al. (2006)
Blood orange (*Citrus sinensis* L. cv. Sanguinelli)	Cy/dp/pn-3-(di)acyl-glu; cy-3-mal-dioxa-glu	Oxa, mal	Cy-3-mal-glu	69	Cebadera-Miranda et al. (2019)
Passion fruit (*Passiflora suberosa*)	Cy/dp/pg/pt-3-6′′-mal-glu	Mal	Pt/cy/dp-mal-glu	27	Kidøy et al. (1997)
Vegetables and tubers					
Broccoli sprouts (*Brassica oleracea* 'Viola')	Cy-3-(di)acyl-diglu-5-glu, cy-3-diacyl-diglu-5-mal-glu	Cou, fer, mal, sin	Cy-3-sin-sin-diglu-5-glu, cy-3-sin-sin-diglu-5-mal-glu	NA	Moreno et al. (2010)
Eggplant (*Solanum melongena*)*	Dp/pt-3-acyl-rut-5-glu	Cou	Dp-3-cou-rut-5-glu (nasunin) or pt-3-cou-rut-5-glu (petanin) depending on the accession	NA	Azuma et al. (2008)
Pigmented potatoes (*Solanum tuberosum* L.)	Cy/dp/mv/pg/pn/pt-3-acyl-rut-5-glu	Caf, cou, fer	Pt-3-cou-rut-5-glu (petanin, in purple potatoes), pg-3-cou-rut-5-glu (in red potatoes)	98	Fossen and Andersen (2000); Giusti et al. (2014); Hillebrand et al. (2009)
Purple carrot (*Daucus carota*)	Cy-3-(2′′-xyl-(6′′-acyl-glu)-gal	Cou, fer, sin	NA	86	Kurilich et al. (2005)
Purple cauliflower (*Brassica oleracea* L. var. Botrytis)	Cy-3-(6-acyl)-sop-5-glu, cy-3-(6-acyl)-sop-5-(6-acyl)-glu	Cou, fer, sin	Cy-3-(6-cou)-sop-5-(6-sin)-glu, cy-3-(6-fer)-sop-5-(6-sin)-glu	43–96	Scalzo et al. (2008)
Purple corn (*Zea mays* L.)	Cy/pn/pg-3-(di)acyl-glu	Mal, suc	Cy-3-mal-glu	30	Lao and Giusti (2016)
Purple pepper (*Capsicum annuum* L.)*	Del-3-acyl-rut-5-glu	Caf, cou, fer	Dp-3-cou-rut-5-glu (nasunin)	97	Sadilova et al. (2006)

(Continues)

TABLE 1 (Continued)

	Types of acylated anthocyanins	Acyl groups	Major acylated anthocyanins	Proportion (%)	References
Purple sweet potato (*Ipomoea batatas* var. P40)	Cy/pn-3-(di)acyl-sop-5-glu	Caf, fer, hba	Pn-3-caf-sop-5-glu, cy-3-caf-hba-sop-5-glu, cy-3-caf-fer-sop-5-glu	91	Xu et al. (2015)
Purple tomato *Del/Ros1*N (*Solanum lycopersicum* cv. MicroTom)**	Dp/pt-3-acyl-rut-5-glu	Caf, cou, fer	Pt-3-cou-rut-5-glu (petanin)	NA	Butelli et al. (2008)
Red cabbage (*Brassica oleracea* L. var. capitata)	Cy-3-(di)acyl-di/triglu-5-glu	Caf, cou, fer, hba	Cy-3-sin-diglu-glu, cy-3-sin-sin-diglu-glu	79	Charron et al. (2007)
Red lettuce (*Lactuca sativa* L.)	Cy-acyl-glu	Mal	Cy-mal-glu	NA	Cheng et al. (2014)
Red curly kale (*Brassica oleracea* L. convar. *acephalaI* var. *sabellica* cv. 'Redbor')	Cy-3-(di)acyl-diglu-5-glu	Cou, fer, sin	Cy-3-sin-fer-diglu-5-glu	NA	Olsen et al. (2010)
Red radish (*Raphanus sativus*)	Pg-3-(di)acyl-sop-5-acyl-glu	Caf, cou, fer, mal	NA	NA	Tamura et al. (2010)
Red onion	Cy-3-(di)acyl-glu	Mal, ace	Cy-3-(6''-mal-glu)	77	Wu et al. (2006)

Note: The proportion of the acylated anthocyanins as part of the total amount of anthocyanins is given as a percentage.
Anthocyanidins: cy, cyanidin; dp, delphinidin; mv, malvidin; pg, pelargonidin; pn, peonidin; pt, petunidin.
Acyl moieties: ace, acetyl; caf, caffeoyl; cou, coumaroyl; hba, hydroxybenzoyl; mal, malonyl; oxa, oxaloyl; sin, sinapoyl; suc, succinyl.
Sugar moieties: glu, glucoside; gal, galactoside; rut, rutinoside; sop, sophoroside; xyl, xyloside.
*Peel.
**Transgenic.
Abbreviation: NA, not available.

genetic, developmental, and environmental factors, such as light and temperature during growth season, which are not all fully understood (Lachman et al., 2009; Liu et al., 2018). Furthermore, potatoes have generally high glycemic index regardless of the variety and cooking method (Ek et al., 2012). Ramdath et al. studied the glycemic indices of purple, red, yellow, and white potato varieties, and no statistically significant differences were found. However, a significant inverse correlation between the glycemic indices and polyphenol content was found (Ramdath et al., 2014).

4 | ASPECTS ON INDUSTRIAL USE

Due to their naturalness, chemical stability, and compelling hues, acylated anthocyanins have potential as food colorants and as a part of functional foods. Anthocyanins may be extracted for food coloring purposes in the EU from vegetables and edible fruits (EU Commission Regulation, 2012). A recent study showed that red and purple potato extracts rich in acylated anthocyanins are noncytotoxic and suitable for food pigmentation; the studied model food was a pasteurized soft drink stored for 30 days at 4 °C. Comparing the drinks colored with the potato extracts and the E163 (grape anthocyanins), the extracts had similar visual and flavor attributes as E163 without off-odors and off-tastes, but the most preferred colorant was the purple potato extract (Sampaio et al., 2020). At room temperature, the aqueous extracts of red and purple potatoes rich in acylated anthocyanins are red until pH 3, colorless at 4–7, and pale yellow-green at 8–10, and after 1 month of storage, 68% and 86% of the color intensity was retained for purple and red potatoes, respectively (Reyes & Cisneros-Zevallos, 2007). When comparing the major monoacylated anthocyanin of purple potatoes, petanin (Section 2, Figure 1), to a common anthocyanin found in berries, cyanidin-3-*O*-glucoside, petanin shows higher color stability and intensity at pH 4–8.1 after 1 h in a buffer at 10 and 23°C. The highest color intensity appeared at pH 1.0 for cyanidin-3-*O*-glucoside and, surprisingly, at pH 8.1 (λ_{max} 577 nm) for petanin. Furthermore, petanin showed better stability during storage (pH 4, 10°C); for example, after 60 days, 84% was still intact, whereas the cyanidin-3-*O*-glucoside was totally degraded. Petanin was concluded to have similar stability when compared to the literature values for other

anthocyanins acylated with an aromatic mono- or diacyl moiety (Fossen et al., 1998).

Extracts rich in acylated anthocyanins could be produced from the waste streams of food industry, such as from pigmented potato peels. Also, synthetic acylation of anthocyanins may be used to gain properties suitable for a certain food product; for example, fatty acids as acyl groups enhance lipophilicity (Yang et al., 2018, 2019); however, synthetic acylation is still being investigated and does not meet the consumer demand for natural colorants. In the end, the applicability or selection of the colorant depends on the targeted hue, the physical conditions of the food matrix, shelf-life, as well as cost and regulatory issues. Moreover, especially in the case of anthocyanins, the value placed on the natural source as well as health effects should be considered when choosing the suitable pigment.

5 | POSTPRANDIAL STRUCTURAL CHANGES

5.1 | Postprandial stability

As reactive compounds, anthocyanins have compromised structural stability and are susceptible to various factors, such as temperature, pH, and light among others (Cabrita et al., 2000; Dangles & Fenger, 2018; Pina et al., 2012). In edible plants, anthocyanins are stable in the mildly acidic conditions of the vacuoles, but the consumption of anthocyanin-rich food exposes anthocyanins to varying pH conditions, physiological temperature, and enzymes of both human and gut microbiota origin, leading to postprandial structural changes. Considering physiological pH, the saliva is neutral (pH 6–7) (Roblegg et al., 2019), the stomach is acidic (pH 2) reaching postprandial pH 5 (Ovesen et al., 1986) or 7 (Dressman et al., 1990), and the pH of duodenum varies between 5 (postprandial) and 6 (fasting) (Dressman et al., 1990). In aqueous media *in vitro*, anthocyanins occur as the red-colored flavylium cations (pH < 2), but increasing pH leads to the formation of blue quinoidal bases (deprotonation) and colorless hemiketals (C-2 hydration and deprotonation) followed by tautomeric processes forming yellow *cis* chalcone from hemiketals, and isomerization of the *cis* chalcone to *trans* chalcone. Also elevated temperatures favor chalcones and thus the loss of color (Brouillard & Delaporte, 1977; Brouillard & Dubois, 1977; Brouillard & Lang, 1990; Dangles & Fenger, 2018; Pina et al., 2012; Santos et al., 1993). It has been suggested that the flavylium cation predominates only in the acidic stomach but not in the intestine and colon (Clifford, 2000; Fleschhut et al., 2006), in which the hemiketal and chalcone structures may prevail; yet, their multifaceted postprandial metabolism and structural changes are not fully understood. Overall, this introduces severe technical and analytical challenges to postprandial investigations of anthocyanins.

Under *in vitro* physical conditions mimicking the human gastrointestinal tract (pH 7.4 and 6.4, 37°C), anthocyanidin aglycones degrade rapidly even without the presence of digestive and microflora enzymes (Fleschhut et al., 2006; Keppler & Humpf, 2005), the hydrolysis of the glycosidic bond at C3-OH being the critical rate-limiting step in the degradation of anthocyanins during digestion. In neutral conditions, chalcone aglycones are further degraded into stable breakdown products; a phloroglucinaldehyde and a phenolic acid whose substitution pattern corresponds to the anthocyanidin in question. The degradation of anthocyanidins occurs via an α-diketone, which is a tautomer of the chalcone aglycone, whereas glycosylation prevents the formation of the α-diketone. Hydroxy and methoxysubstituents in the B-ring decrease the stability of anthocyanidin aglycones and thus increase the degradation in neutral conditions. Glycosyl and acyl moieties, however, stabilize the anthocyanidins even under neutral pH conditions (Fleschhut et al., 2006).

Acylation enhances the stability of anthocyanins compared to nonacylated ones depending on the acyl group (aromatic or aliphatic acid and its structure and size), their number, and their attachment sites. Acylation by aromatic acids (hydroxycinnamic acids and hydrox-ybenzoic acids) stabilizes the anthocyanins via intramolecular and/or intermolecular copigmentation, self-association reactions, decreased polarity, and steric hindrance against the nucleophilic attack of water to the C-2 of the flavylium nucleus, whereas acylation with aliphatic acids may stabilize via steric hindrance depending on the aliphatic acid (Bakowska-Barczak, 2005; Cevallos-Casals & Cisneros-Zevallos, 2004; Dangles et al., 1993; Dangles & Fenger, 2018; Fossen et al., 1998; Giusti & Wrolstad, 2003; Nerdal & Andersen, 1991; Yoshida et al., 1992; Zhao et al., 2017). Enhanced stability is detected also under simulated gastrointestinal conditions *in vitro* (McDougall et al., 2007; Oliveira, Perez-Gregório, et al., 2019). In general, anthocyanins carrying two or more aromatic acyl groups are more stable than the monoacylated ones (Mazza & Brouillard, 1987) as they form intramolecular sandwich-type stacking via hydrophobic interactions where two aromatic acids shelter the anthocyanidin nucleus from nucleophilic attack of water to C-2 (Brouillard, 1981; Yoshida et al., 1992). Monoacylated petanin, instead, is stabilized via intermolecular stacking of petunidin aglycones as well as *p*-coumaroyl moieties to prevent the hydration of C-2 and the formation of the colorless chalcones (Nerdal & Andersen, 1991, 1992). However, the extent of inter- and intramolecular copigmentation and self-association of

acylated anthocyanins under physiological conditions is not fully understood.

5.2 | Absorption, metabolism, distribution, and excretion

In addition to the structural modifications driven by the physiological environment of the gastrointestinal tract, anthocyanins are subjected to digestive enzymes and xenobiotic phase I and II metabolism. Phase I reactions include, for example, oxidation and reduction, whereas phase II metabolism involves conjugation reactions with methyl, glucuronic acid, and sulfate groups in the enterocytes of small intestine and hepatocytes of liver (Cardona et al., 2013).

In *the mouth*, chewing anthocyanin-rich food with the teeth releases the anthocyanins from the vacuolar structures and mixes the food bulk with saliva. Considering nonacylated anthocyanins, they are hydrolyzed into their aglycones in human saliva (Kamonpatana et al., 2012, 2014; Mallery et al., 2011). Nevertheless, the spontaneous reactions related to pH and physiological temperature described in the previous section, the primary hydrolysis mechanism is enzymatic as the heat-inactivated saliva, cell-free saliva, and enzyme-free artificial saliva induced less degradation of cyanidin glycosides compared to intact saliva at a physiological pH and temperature *ex vivo* (Kamonpatana et al., 2012). The enzymatic hydrolysis is caused by the *β*-glucosidase of saliva, oral epithelium, and oral microbiota (Mallery et al., 2011) of which microbiota contributes the most at 37 °C both *in vivo* and *ex vivo* (Kamonpatana et al., 2012, 2014). Interestingly, the sugar moiety and the anthocyanidin aglycone affect the efficiency of the hydrolysis reaction; incubation of nonacylated anthocyanin glycosides in human saliva *ex vivo* degraded more glycosides of delphinidin and petunidin than those of cyanidin, malvidin, and peonidin (Kamonpatana et al., 2012). After retaining chokeberry or red grape juice for 5 min in the oral cavity of humans, the loss of cyanidin xyloside of chokeberry juice was greater when compared to galactoside, glucoside, and arabinoside of cyanidin, and delphinidin glucoside in red grape juice, which degraded more than the glucosides of cyanidin, petunidin, peonidin, and malvidin (Kamonpatana et al., 2014). Monosaccharides are more susceptible to hydrolysis when compared to di- and trisaccharides as detected after incubating fruit and berry extracts rich in nonacylated anthocyanins *ex vivo* in human saliva (Kamonpatana et al., 2012). The comparison of the stability of acylated and nonacylated anthocyanins by incubating extracts of purple sweet potatoes rich in acylated anthocyanins and grape skin rich in nonacylated anthocyanins in human saliva *ex vivo* for 10 min showed no difference in stability regardless of whether matrix components of purple sweet potato or red wine were added or not (Oliveira, Perez-Gregório, et al., 2019).

The stomach is an important site of absorption for anthocyanin glycosides as evidenced by several authors detecting nonacylated anthocyanins in plasma shortly after ingestion, both in human volunteers (Cao et al., 2001; Cao & Prior, 1999; Milbury et al., 2002) and animal models (Felgines et al., 2003; Passamonti et al., 2003; Talavéra et al., 2003, 2005; Tsuda et al., 1999). The molecular mechanism behind the transport of anthocyanins from the lumen of the stomach into the gastric mucosa involves an organic anion membrane carrier, bilitranslocase, located in the epithelial cells of the gastric mucosa. Structurally different anthocyanins may act as its substrates as studied *in vitro* yet anthocyanin monoglucosides (K_1 1.4−8.6 μM) and diglucosides (K_1 5.8−6.8 μM) better than the aglycones (K_1 5.3−22.2 μM). Acylation decreases the affinity; the K_1 of malvidin-3-*O*-(6-*O*-acetoyl)-*β*-glucoside (K_1 58.3 μM) was decreased by 41-fold when compared to that of malvidin glucoside (1.4 μM). Interestingly, acylation by a hydroxycinnamic acid (malvidin-3-*O*-(6-*O*-*p*-coumaroyl)-*β*-glucoside) did not show affinity at all, possibly due to steric hindrance (Passamonti et al., 2002). An *in vitro* study with a gastric cell model, MKN-28 cell line, showed that the glucose transporters GLUT1 and GLUT3 may contribute to the gastric uptake of red wine anthocyanins by binding the B-ring or glucose, but also monocarboxylate transporter MCT1 was expressed on the cells (Oliveira et al., 2015). Another *in vitro* study conducted with a nano-based silencing approach and MKN-28 cells showed that GLUT1, GLUT3, and other yet unknown transporters are involved in the transportation of both nonacylated and acylated anthocyanins, but multiple glycosyl and acyl groups decrease the transportation efficiency as detected with purified mono- and diacylated purple sweet potato peonidin-derived anthocyanins (7−8%) compared to nonacylated malvidin-3-*O*-glucoside (10%) (Oliveira, Roma-Rodrigues, et al., 2019).

Regardless of the decreased transport efficiency *in vitro*, the rapid peaking of acylated anthocyanins in rodents suggests that stomach is involved in the absorption of acylated anthocyanins. After oral administration of a purified acylated anthocyanin, nasunin from eggplant (delphinidin-3-*p*-coumaroyl-rutinoside-5-glucoside), it peaked rapidly as intact in rat plasma 15 min postprandially, showing similar absorption with delphinidin-3-glucoside (Ichiyanagi et al., 2006). Likewise, a cyanidin-derived monoglycoside acylated with a malonic acid was similarly absorbed as cyanidin-3-glucoside in rats after in situ gastric administration of red orange anthocyanin extract (Felgines et al., 2006). The major anthocyanin of the

purple sweet potato, peonidin-3-caffeoyl-sophoroside-5-glucoside, administered orally by direct stomach intubation as purple sweet potato anthocyanin concentrate, was absorbed as such in rats (Suda et al., 2002). After ingesting purple sweet potato extract containing eight acylated anthocyanins, only two of them, cyanidin and peonidin derivatives of caffeoyl-sophoroside-glucoside, were rapidly absorbed in rats peaking at 5 min after ingestion. The same two anthocyanins were detected in human plasma, but the six other ingested diacylated anthocyanins were not, suggesting structure-dependent absorption (Harada et al., 2004). *In vitro*, malvidin-3-*O*-(6-*O*-coumaroyl)-glucoside-5-*O*-glucoside extracted from red wine showed similar absorption in a human gastric cell model, MKN-28, as its nonacylated counterpart (Han et al., 2020).

Considering stability, the acylated anthocyanins of purple potatoes (Kubow et al., 2017), purple sweet potatoes (Kubow et al., 2016; Oliveira, Perez-Gregório, et al., 2019), and red cabbage (McDougall et al., 2007; Podsędek et al., 2014) are stable in simulated *in vitro* gastric conditions and are further released from the food matrix (Podsędek et al., 2014). In an *in vitro* model simulating gastric conditions, the amount of the nonacylated grape skin anthocyanins was slightly decreased, but the purple-sweet potato anthocyanins not; the difference did not reach statistical significance (Oliveira, Perez-Gregório, et al., 2019).

The small intestine introduces another important absorption site for anthocyanin glycosides, such as cyanidin-3-glucoside and cyanidin-3-rutinoside, as detected in rat studies (Hassimotto et al., 2008; Talavéra et al., 2004). *In vitro*, a mouse jejunum set into a Ussing chamber has been shown to be the major absorptive part of the small intestine for nonacylated cyanidin-3-glucoside with only a little contribution from the duodenum and none from the ileum (Matuschek et al., 2006). Anthocyanin glycosides are absorbed *in vitro* into an everted rat jejunum sac model as detected with cyanidin-3-glucoside and cyanidin-3-rutinoside, but the corresponding aglycone, cyanidin, is not. Passive diffusion of the unstable aglycone did not occur regardless of its high lipophilicity (Hassimotto et al., 2008). The transport mechanism of the nonacylated anthocyanin glycosides to the enterocytes may involve the brush-border glucose transporter GLUT2 and sodium-glucose cotransporter SGLT1 (Faria et al., 2009; Hahm et al., 2021; Hassimotto et al., 2008; Mülleder et al., 2002; Zou et al., 2014). *In vivo*, Mülleder et al. showed evidence of the intestinal glucose transportation system in healthy volunteers as a simultaneous consumption of glucose and elderberry extract rich in cyanidin-3-glucoside and cyanidin-3-rutinoside resulted in a lower excretion of anthocyanins into the urine when compared to the extract alone (Mülleder et al., 2002). Also, acylated anthocyanins may permeate the intestinal barrier as investigated with purple carrot anthocyanins and Caco-2 cells *in vitro*, but their transport efficiency was lower than that of nonacylated anthocyanins (Olejnik et al., 2016). Interestingly, a recent study showed that both nonacylated and acylated anthocyanins from purple carrots may be absorbed from rat jejunum via an organic anion transporting polypeptide transporter, but the acylated anthocyanins were not absorbed by GLUT2 (Hahm et al., 2021). On the contrary, another study showed that glucose transporters may be involved in the transport of acylated anthocyanins, as glucose inhibited the absorption of acylated purple sweet potato anthocyanins *in vitro* (Oliveira, Perez-Gregório, et al., 2019). The acylated purple potato and purple carrot anthocyanins were reported to be absorbed (6 ± 1% and 36 ± 6%, respectively) into human intestine cell model, Caco-2, via glucose transporters, *in vitro* (Zhang et al., 2017).

The structures of anthocyanins affect their transport efficiency; more methoxy groups and less hydroxy substituents in the B-ring enhance the transport of anthocyanins to Caco-2 cells *in vitro* as the transportation of malvidin glucoside was the highest and that of delphinidin glucoside was the least efficient among the seven nonacylated blueberry anthocyanins studied (glucosides of cyanidin, delphinidin, petunidin, peonidin, and malvidin, galactosides of cyanidin and peonidin), and the glucosides were absorbed more than the galactosides (Yi et al., 2006). In situ perfusion in rats, however, showed that cyanidin glucoside was absorbed more than malvidin glucoside, and cyanidin rutinose was absorbed less than cyanidin glucoside (Talavéra et al., 2004). The acylation of cyanidin-3-(6′′-malonyl)-glucoside interestingly favored the intestinal absorption over nonacylated cyanidin-3-glucoside in rats (Felgines et al., 2006). *In vitro*, malvidin-3-*O*-(6-*O*-coumaroyl)-glucoside-5-*O*-glucoside was absorbed similarly as its nonacylated counterpart in human enterocyte Caco-2 model cells (Han et al., 2020). In healthy volunteers, acylated anthocyanins from purple carrots were shown to have a shorter mathematically modeled half-life of absorption to plasma in the upper gastrointestinal tract than the nonacylated ones, suggesting a shorter absorption site of acylated anthocyanins (Novotny et al., 2012).

Considering stability, the lactase phloridzin hydrolase (a β-glucosidase) may hydrolyze anthocyanin monoglucosides in the small intestine as hydrolysis of cyanidin-3-glucoside, but not cyanidin-3-rutinoside, was detected in rats (Hassimotto et al., 2008). Acylated anthocyanins of purple potato, purple sweet potato, and red cabbage may be hydrolyzed as their amount decreased in a vessel simulating small intestine without a cellular absorption model (Kubow et al., 2016, 2017; McDougall et al., 2007; Podsędek et al., 2014). The red cabbage anthocyanins

acylated with a sinapic acid were more vulnerable to degradation in comparison to those acylated with other hydroxy-cinnamic acids (McDougall et al., 2007). After the *in vitro* gastrointestinal digestion of a polyphenolic purple tomato extract, the simulated conditions of small intestine did not affect the total amount of acylated anthocyanins of purple tomatoes, but the gastric conditions unexpectedly did, resulting in the total loss of 39% of the parent anthocyanins and 37% of the total phenolic contents. No anthocyanin degradants were detected but unidentified phenolic metabolites were (Li et al., 2014). Comparing the nonacylated and acylated anthocyanins, the simulated small intestinal conditions decreased 27−43% of the acylated purple sweet potato anthocyanins (22−31% with food matrix), but the reduction was 49−52% and 30−45% for the nonacylated red wine anthocyanins without and with the matrix components, respectively (Oliveira, Perez-Gregório, et al., 2019).

The colon is not known to absorb anthocyanins (Matuschek et al., 2006). However, the colon is an essential part of the postprandial metabolism of anthocyanins as large amounts of nonabsorbed anthocyanins reach the colon and are exposed to microbial and endogenous β-glycosidase (Hassimotto et al., 2008; Keppler & Humpf, 2005). Intact acylated anthocyanins may reach the colon as studied with freeze-dried purple potato powder (71.8 ± 0.3%), freeze-dried purple carrot powder (45 ± 1%) (Zhang et al., 2017), purple tomato extract (61%) (Li et al., 2014), and red cabbage extract (25%) (McDougall et al., 2007) after simulated *in vitro* gastric and intestinal digestion. The colonic microbiota rapidly hydrolyzes anthocyanin glycosides, such as glucosides, diglucosides, and rutinosides, as the pure compounds or anthocyanin-rich extracts were investigated *in vitro* by fermenting the gut microbiota isolated from pig caecum (Keppler & Humpf, 2005), and the fecal suspensions of rats (Hassimotto et al., 2008) and human volunteers (Fleschhut et al., 2006; Aura et al., 2005; González-Barrio et al., 2011; Hidalgo et al., 2012). Microbial metabolism also leads to the cleavage of the heterocyclic C-ring (Aura et al., 2005; Hidalgo et al., 2012). As the hydrolyzed aglycones are not stable in the neutral pH of the colon, they are broken down to phenolic acids corresponding to the substitution pattern of the B-ring of the parent anthocyanidin in question; for example, protocatechuic acid is formed from cyanidin, vanillic acid from peonidin, and syringic acid from malvidin (Fleschhut et al., 2006; Hassimotto et al., 2008; Keppler & Humpf, 2005). Other phenolic metabolites resulting from the microbial activity include, for example, catechol, pyrogallol, hydrox-ybenzoic acids, propionic acids, gallic acid, and *p*-coumaric acid (González-Barrio et al., 2011; Hidalgo et al., 2012). The phenolic metabolites show enhanced stability under neutral pH conditions as compared to anthocyanins, and methoxysubstituted phenolic acids may be *O*-demethylated, thus possibly leading to increased antioxidant properties (Keppler & Humpf, 2005). The uptake mechanism of these metabolites (e.g., benzoic and hydrox-ybenzoic acid) may involve MCT1, the monocarboxylate transporter 1 (Haughton et al., 2007).

Human gut microbiota is able to break down acylated anthocyanins: pelargonidin sophorosides acylated with hydroxycinnamic and/or malonic acids were degraded to 4-hydroxybenzoic acid and hydrox-ycinnamic acids *in vitro* (Fleschhut et al., 2006). The acylated anthocyanins of cooked, freeze-dried, and milled purple potatoes (Kubow et al., 2017) and red cabbage extract (Podsędek et al., 2014) were degraded by the human gut microbiota in an *in vitro* gastrointestinal model. *In vitro* incubation of Concord grape juice rich in both nonacylated and acylated anthocyanins (*O*-acetyl glycosides, *O*-*p*-coumaroyl-*O*-diglucosides, *O*-*p*-coumaroylglucosides) in human feces resulted in a variety of phenolic acids, such as phenylacetic acids, phenyllactic acids, and hydrox-ybenzoic acids, and simple phenolic degradants catechol, resorcinol, pyrogallol, and phloroglucinol (Stalmach et al., 2013). In healthy humans, a meal supplemented with a purple potato extract leads to the detection of a variety of phenolic compounds both in urine and plasma (Jokioja et al., 2021).

When compared to nonacylated anthocyanins, the acylated anthocyanins may be more readily degraded by the gut microbiota. After a 12-week chronic intake of a Concord grape supplement rich in acylated anthocyanins by obese mice, the content of total anthocyanins in feces was increased by a 10-fold compared with the feces collected during a late test week when antibiotics were administered to knock down the gut microbiota. The change was greater than that observed after the intake of berry supplements rich in nonacylated anthocyanins (Overall et al., 2017). Cyanidin-3-(6′′-malonyl)-glucoside is likely to be more readily available for microbial degradation in rats than its nonacylated counterpart as the ratio of these two anthocyanins in the cecal contents was changed to favor the nonacylated anthocyanin when compared to the ratio in the food origin, red orange juice (Felgines et al., 2006).

In colon, acylated anthocyanins may affect the gut microbiota composition, but more studies are still needed to compare the effects of structurally different anthocyanins. Incubating purple sweet potato extract rich in diacylated anthocyanins in feces of healthy human volunteers *in vitro* showed probiotic effects as the extract enhanced the growth of *Bifidobacterium* and *Lactobacillus/Enterococcus* spp. and decreased the growth of *Prevotella*, *Clostridium histolyticum*, and *Bacteroides* without affecting the total number of bacteria. Also, the total concentration of produced short-chain fatty acids

was increased (Zhang, Yang, et al., 2016). A 12-week daily supplementation of high-fat diet (HFD) with Concord grape supplement rich in acylated anthocyanins resulted in elevated levels of *Actinobacteria* in obese mice; even more than with other berry supplements (blackberry, black currant, black raspberry, blueberry, and Maqui berry) (Overall et al., 2017).

Phase I and II metabolism reactions occur in addition to the structural changes described above. In a clinical intervention, pelargonidin was detected in urine even though it was not ingested, suggesting the interconversion of anthocyanidins during human postprandial metabolism (Kalt et al., 2014). This may be due to cytochrome P450 isoforms, which remove methyl groups and add hydroxy groups (phase I), and in phase II metabolism, methyl groups may be added to hydroxy groups to form methoxy-groups (Kalt et al., 2014; Wu et al., 2011). The phase II mechanism is an important pathway occurring in the intestinal epithelial cells of small intestine and colon walls (Fang, 2014; Wu et al., 2011). Anthocyanins are conjugated to a large extent with a glucuronic acid via uridine 5′ diphosphate-glucuronosyltransferases, a methyl group via catechol-*O*-methyl transferase, and a sulfate via sulfotransferase (Kalt, 2019), as detected in several studies involving human volunteers (Czank et al., 2013; de Ferrars, Czank, Zhang, et al., 2014; Felgines et al., 2003; Kalt et al., 2014). The anthocyanin glucuronides may be transferred through the gastric and small intestine walls, possibly with the same transportation mechanisms similar to the nonconjugated anthocyanins, as malvidin glucuronide appeared in the basolateral side of *in vitro* model cells (MKN-28 and Caco-2) with similar transport efficiency as nonconjugated malvidin (di)glucosides extracted from red wine (Han et al., 2020). The urinary concentration of the anthocyanin degradants and conjugates exceeds the amount of parent compounds; a 24-fold increase was detected after an intake of bilberry juice by healthy volunteers (Kalt et al., 2014).

Acylated anthocyanins may also undergo methylation in phase II metabolism, as cyanidin-3-(6′′-malonyl)-glucoside of red orange juice lyophilizate was methylated in rat metabolism and excreted via urine like its nonacylated counterpart (Felgines et al., 2006), and methylated monoacylated (caffeic, sinapic, and ferulic acids) cyanidin triglucosides were found in postprandial plasma and urine of healthy volunteers after a meal of fresh and fermented red cabbage (Wiczkowski et al., 2016). Glucuronidation of intact acylated anthocyanins has not been reported; for example, nasunin was not methylated nor glucuronidated in rat metabolism (Ichiyanagi et al., 2006). Clinical interventions feeding steamed and microwaved red cabbage (Charron et al., 2007), fresh and fermented red cabbage (Wiczkowski et al., 2016), and grape juice (Stalmach et al., 2011) rich in both acylated and nonacylated anthocyanins report only nonacylated anthocyanins conjugated with a methyl, glucuronide, or diglucuronide, giving evidence that the acyl groups may be cleaved prior to conjugation and only the nonacylated anthocyanins undergo conjugation. The phenolic degradants are conjugated in phase II metabolism as well, as detected with *in vitro* in a gastrointestinal model (Woodward et al., 2011) and in human volunteers (Czank et al., 2013).

Enterohepatic circulation has been suggested to occur due to the persistence of anthocyanin conjugates in human urine up to 24 h (de Ferrars, Czank, Zhang, et al., 2014; Kalt et al., 2014; Kay et al., 2004) and 48 h (Czank et al., 2013), and the second rise of anthocyanin concentration in plasma (Fang, 2014). Generally, the absorbed xenobiotics in the portal vein are transferred to the liver for phase II conjugation. Then, they are transported back to the small intestine via bile instead of released to systemic circulation. In the small intestine, the metabolites may be deconjugated, absorbed, and transported to the liver (Roberts et al., 2002). In animal studies, anthocyanins and anthocyanin phase II conjugates have been detected from the liver after absorption (Felgines et al., 2010; Marczylo et al., 2009; Passamonti et al., 2005; Talavéra et al., 2005; Tsuda et al., 1999), as transferred from the portal circulation via bilitranslocase (Passamonti et al., 2005), and from bile (Marczylo et al., 2009). Liver may continue the phase II conjugation of anthocyanins, as detected in a rat study reporting methylation of the B-ring of cyanidin-3-glucoside (catechol) in liver, possibly with catechol-*O*-methyltransferase (Tsuda et al., 1999). Liver may also break down anthocyanins to phenolic acids and further produce their phase II conjugates as studied with human liver microsomes (Woodward et al., 2011). From enterohepatic circulation, anthocyanins and their metabolites are transferred to systemic circulation.

In *blood (plasma or serum)*, anthocyanins appear quickly; the maximum concentration (C_{max}) of anthocyanins in humans is reached within 0.50−4 h after an anthocyanin-rich meal in nanomolar concentrations (Table 2). In humans, anthocyanins have been found as such and, for example, also as glucuronides of both aglycones and glycosides, sulfated aglycones, and methylated aglycone and glycoside glucuronides (Banaszewski et al., 2013; Czank et al., 2013; de Ferrars, Cassidy, et al., 2014; Kay et al., 2005; Kuntz et al., 2015; Matsumoto et al., 2001; Mullen et al., 2008; Wiczkowski et al., 2016). Considering acylated anthocyanins, some of purple sweet potatoes (two out of eight) (Harada et al., 2004) and red cabbage (16 out of 18) (Wiczkowski et al., 2016) but none after a meal supplemented with a purple potatoes extract (Jokioja et al., 2021) have been detected in clinical trials. Anthocyanins are further degraded into phenolic metabolites (Section 5.3).

TABLE 2 An overview of the pharmacokinetics of anthocyanins after one meal in healthy volunteers

Food	*n*	Dose (mg)	Recovery (%, urine)	t_{max} (h, urine)	C_{max} (nM, plasma)	t_{max} (h, plasma)	References
Bilberry (extract)	5	2 225	0.03/24 h	2–4	27 ± 11a 43 ± 21b	1.4 ± 0.5 2.2 ± 1.1	Mueller et al. (2017)
Black currant (juice)	14	716 1239 746e	0.048/4 h 0.07/4 h 0.045/4 h	NA NA NA	NA NA NA	0.75 0.75 1.5	Nielsen et al. (2003)
Blueberry (powder)*	5	1200f	0.002–0.003/4 h (plasma)	NA	29.1 ± 6.1	4	Mazza et al. (2002)
Elderberry (capsule)	26	500	NA NA	2–3d 2–3e	7c 16d	2d 2e	de Ferrars, Cassidy, et al. (2014)
Purple carrot (juice)*	10	65 194 323	NA NA NA	NA NA NA	2.5 ± 0.6 6.6 ± 1.3 9.6 ± 1.7	2 1 2	
Purple carrot (raw or cooked)*	12	208 (raw) 160 320	0.140, **0.013**/24 h 0.190, **0.014**/24 h 0.100, **0.008**/24 h	4 4 4	5.8 ± 1.7 5.3 ± 1.9 5.0 ± 1.4	2 22	Kurilich et al. (2005)
Red grape (juice)*	9	284	0.23	0.5	223	0.5	Bitsch et al. (2004)
Red wine	9	280	0.18	1.5	96	1.5	Bitsch et al. (2004)
Purple sweet potato (beverage)*	6	311	**0.01–0.03**/24 h	0–5	2.0	1.5	Harada et al. (2004)
Red cabbage (microwave-cooked)*	12	62 124 186	0.176, **0.041**/24 h 0.105, **0.023**/24 h 0.085, **0.020**/24 h	2–4 2–4 2–4	NA	NA	Charron et al. (2007)

Note: The recoveries of acylated anthocyanins are bolded.

C_{max}, maximum concentration.

t_{max}, time point of maximum concentration.

*contains acylated anthocyanins.

Abbreviation: NA, not analyzed.

a, malvidin-3-*O*-glucoside; b, peonidin-3-*O*-glucoside; c, cyanidin-3-*O*-glucoside; d, cyanidin-3-*O*-sambubioside; e, with carbohydrates; f, with high-fat meal.

Target tissues are reached as the systemic circulation transports anthocyanins further to kidneys (Felgines et al., 2010; Marczylo et al., 2009; Talavéra et al., 2005; Tsuda et al., 1999; Vanzo et al., 2011), brain (Talavéra et al., 2005), lung, heart, and prostate (Marczylo et al., 2009) as studied with rodent models and nonacylated anthocyanins. The transportation to target tissues is fast: after 15 s of administration, the nonacylated cyanidin-3-glucoside was detected in plasma, kidney, and liver, and almost disappeared from plasma before 1 min in rats (Vanzo et al., 2011). The uptake of acylated anthocyanins to tissues may differ from that of nonacylated ones as the intraruminally administrated red cabbage lyophilizate in 5% ethanol leads to the detection of both anthocyanin types in urine and plasma, but only nonacylated anthocyanins were detected in the cerebrospinal fluid of sheep (Platosz et al., 2020). The uptake of acylated anthocyanins to tissues should be investigated more thoroughly in the future.

Urine, feces, and breath are the excretion routes of anthocyanins and anthocyanin metabolites in humans as detected after acute consumption of $^{13}C_5$-cyanidin-3-*O*-glucoside (Czank et al., 2013; de Ferrars, Czank, Zhang, et al., 2014). The major excretion route at 0–6 h was urine, whereas at 6–24 h, it was feces. The maximum rate of elimination in breath occurred at 6 h. Furthermore, the urinary concentrations of parent anthocyanins exceeded those in plasma by 30-fold (Czank et al., 2013).

The urinary recoveries of the parent anthocyanins in healthy humans after one meal are well below 1%, which is further decreased by acylation. The t_{max} varies from 0.75 to 5 h (Table 2). In urine, nonacylated anthocyanins have been detected both as aglycones and glycosides and their glucuronides and methyl glucuronides, and also as aglycone diglucuronides and anthocyanin (di)sulfates, but mostly as glucuronidated or methylated aglycones after a meal of pureed strawberries (Carkeet et al., 2008), elderberry extract (de Ferrars, Cassidy, et al., 2014), strawberries (Felgines et al., 2003; Mullen et al., 2008), elderberry extract and lowbush blueberry (Wu et al., 2002), blackberries (Felgines et al., 2005), blueberry juice (Kalt et al., 2014), chokeberry extract (Kay et al., 2005), and red grape/blueberry juice and smoothie (Kuntz et al., 2015).

Clinical trials feeding purple potatoes (Tsang et al., 2015), purple potato extract (Jokioja et al., 2021), and Concord grape juice (38% of acylated anthocyanins) (Stalmach et al., 2011) did not detect acylated anthocyanins in human urine, but other trials detected acylated anthocyanins after the intake of a beverage prepared from a purple sweet potato extract (two out of eight [Harada et al., 2004] and one out of seven [Oki et al., 2006]), steamed and microwaved red cabbage (8 out of 30 [Charron et al., 2007], fresh and fermented red cabbage (16 out of 18 [Wiczkowski et al., 2016]), and raw and microwave-cooked purple carrot (two out of three) (Kurilich et al., 2005), suggesting structure-dependent absorption. In rats, a 3-month feeding with grape anthocyanin-rich extract containing a mix of acylated (22%) and nonacylated anthocyanins leads to the detection of one acylated anthocyanin out of three (petunidin-3-coumaroyl-glucoside) (He et al., 2006). The excretion of acylated anthocyanins to feces has been studied with rats fed with anthocyanin-rich extract from grapes for 14 weeks containing *p*-coumaroyl-glucosides of petunidin, malvidin, and delphinidin. Both the acyl group and diglycosylation enhance the stability of the anthocyanins in the gut when compared to nonacylated or monoglycosylated grape anthocyanins, leading to increased amount of acylated anthocyanins in the feces (He et al., 2005).

In general, the bioavailability of anthocyanins in humans is affected by several factors, such as their structural characteristics (McGhie et al., 2003; Nielsen et al., 2003; Novotny et al., 2012), dosage (Carkeet et al., 2008; Charron et al., 2007, 2009; Kurilich et al., 2005), simultaneously ingested other foods and nutrients (Mullen et al., 2008; Nielsen et al., 2003), food matrix and food processing (Charron et al., 2009; Kurilich et al., 2005; Nurmi et al., 2009; Wiczkowski et al., 2016) as recently reviewed (Eker et al., 2020). Considering acylated anthocyanins, the food matrix did not affect the total recovery of acylated cyanidin-based anthocyanins of purple carrots whether the carrots were served raw, microwave-cooked, or juiced (Charron et al., 2009; Kurilich et al., 2005). The nonacylated counterparts, however, were recovered less from plasma and urine after microwave cooking as compared to raw carrots (Kurilich et al., 2005). Even though the whole carrots and carrot juice provided similar amounts of total anthocyanins in the plasma, the anthocyanins were absorbed quicker after the meal of carrot juice (Charron et al., 2009; Kurilich et al., 2005). Fermentation affects the bioavailability as the recovery of acylated anthocyanins from human plasma after the acute intake of fresh red cabbage was 10% higher than that of fermented cabbage (Wiczkowski et al., 2016). The bioavailability of acylated anthocyanins might be affected by other compounds ingested simultaneously; in an *in vitro* gastrointestinal model, digesting crushed pigmented red cabbage simultaneously with crushed carotenoid-rich tomatoes or spinach enhanced the recovery of anthocyanins by 10–15% (Phan et al., 2019).

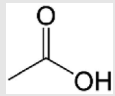
5.3 | Degradation

Recent postprandial clinical trials indicate that nonacylated anthocyanins are spontaneously and/or enzymatically degraded into phenolic metabolites. The detected phenolic metabolites contain different phenolic acids, aldehydes, alcohols, acetic acids, propanoic acids, and hydrox-ycinnamic acids, which may be further subjected to phase II conjugation (Czank et al., 2013; de Ferrars, Cassidy, et al., 2014; de Ferrars, Czank, Zhang, et al., 2014; Mueller et al., 2017). The total concentration of these metabolites is high; a 42-fold (Czank et al., 2013) and 45-fold (de Ferrars, Cassidy, et al., 2014) (plasma) and 60-fold (de Ferrars, Cassidy, et al., 2014) (urine) increase has been reported when compared to the parent anthocyanins after an intake of elderberries (de Ferrars, Cassidy, et al., 2014) or ^{13}C-labeled cyanidin-3-*O*-glucoside (Czank et al., 2013).

However, there is still a gap in understanding the *in vivo* degradation of acylated anthocyanins. In the study of Tsang et al. (2015), five healthy volunteers consumed a meal of purple potatoes but only some urinary phenolic metabolites were tentatively identified. Another study showed a vast diversity of phenolic degradants and metabolites after a meal of purple potato extract both in urine and less in plasma (Jokioja et al., 2021). Two studies have investigated the phenolic metabolites after a meal of Concord grape juice containing a mix of nonacylated and acylated anthocyanins (Stalmach et al., 2011, 2013).

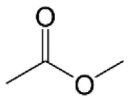
As the number of studies investigating the degradants of acylated anthocyanins is low, the phenolic metabolites of foods containing both nonacylated and acylated anthocyanins are summarized in Table 3 from the relevant postprandial clinical interventions (2009–2021) conducted with healthy volunteers. Nevertheless, drawing conclusions about the degradation of structurally different anthocyanins into phenolic metabolites on the basis of the current literature is challenging as the studies differ in design and analytical methods: for example, in the anthocyanin source and food matrix (purified anthocyanin, anthocyanin-rich extract, or whole food), dose of anthocyanins, type of anthocyanins (one or mixed), type of meal (mixed meal or not), and other compounds in the dietary anthocyanin source possibly metabolizing similarly and/or affecting the absorption and metabolism of anthocyanins.

TABLE 3 Suggested phenolic metabolites of acylated and nonacylated anthocyanins reported in recent clinical interventions (2009–2021) serving an acute anthocyanin-rich meal to healthy volunteers

Metabolite	Benzene ring substituents			Functional group in C1 of benzene	C_{max} (nM)	t_{max} (h)	Detected in:		
	OH	OCH_3	Others				Urine	Blood	Feces
Benzoic acids and hydrox-ybenzoic acids									
Benzoic acid	–	–	–		2169 ± 608d	8.6 ± 3.0d	d	d	–
2,3-Dihydroxybenzoic acid	2,3-OH	–	–		12024 ± 4055d	7.3 ± 3.2d	bdg	dg	ab
2,4-Dihydroxybenzoic acid	2,4-OH	–	–		22 ± 4	5.1 ± 2.4d	dg	d	–
2,5-Dihydroxybenzoic acid	2,5-OH	–	–		425 ± 137	4.4 ± 0.3d	d	d	–
2,6-Dihydroxybenzoic acid	2,6-OH	–	–		–	–	g	g	–
3,4-Dihydroxybenzoic acid (protocatechuic acid)	3,4-OH	–	–		146 ± 74a; 109 ± 45d; 81 ± 32h; 7.6 ± 1.8n; 4.5 ± 0.5o; 7.9 ± 2.9p	3.3 ± 0.7a; 2.0 ± 0.6d; 1.0 ± 0.0h; 57 ± 5n; 63 ± 8o; 1.8 ± 1.3p	ac–gikp	a–e,g–ip	abe
3,5-Dihydroxybenzoic acid	3,5-OH	–	–		–	–	bc	bc	–
Gallic acid	3,4,5-OH	–	–		25 ± 12h	1.4 ± 0.5h	gp	gh	–
Gallic acid-4-*O*-glucuronide	3,4,5-OH		4-*O*-glc				p	–	–
2-Hydroxybenzoic acid	2-OH	–	–		308 ± 128d	6.3 ± 3.3d	bd	bd	–
3-Hydroxybenzoic acid	3-OH	–	–		66 ± 23d; 214.3 ± 123.7p	6.1 ± 2.4d; 1.4 ± 1.3p	abdmp	bdp	a
3-Hydroxybenzoic acid glucuronide	–	–	3-*O*-glc		–	–	g	–	–
3-Hydroxybenzoic acid sulfate	–	–	3-*O*-s		–	–	k	–	–
4-Hydroxybenzoic acid	4-OH	–	–		42 ± 7d; 214.3 ± 123.7p	5.3 ± 2.5d; 1.4 ± 1.3p	abcdfgkp	bdgp	ab
4-Hydroxybenzoic acid glucuronide	–	–	4-*O*-glc		–	–	g	–	–
4-Hydroxybenzoic acid sulfate	–	–	4-*O*-s		–	–	gk	–	–
2-Hydroxy-4-methoxybenzoic acid	2-OH	4-OCH_3	–		–	–	e	bce	be
Isovanillic acid	3-OH	4-OCH_3	–		195a**; 220 ± 44d	2.0a**; 9.8 ± 3.6d	adegp	ade	abe

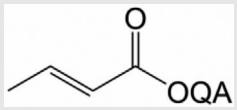
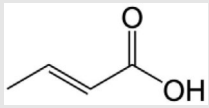
(Continues)

TABLE 3 (Continued)

Metabolite	Benzene ring substituents			Functional group in C1 of benzene	C_{max} (nM)	t_{max} (h)	Detected in:		
	OH	OCH_3	Others				Urine	Blood	Feces
Isovanillic acid-3-*O*-glucuronide	–	4-OCH_3	3-*O*-glc		35 ± 5a	4.3 ± 0.6a	abceg	abceg	abe
Isovanillic acid-3-*O*-sulfate	–	4-OCH_3	3-*O*-s		–	–	abeg	be	abe
2-Methoxybenzoic acid	–	2-OCH_3	–		–	–	p	–	–
3-*O*-Methyl gallate	3,4-OH	5-OCH_3	–		79 ± 25h	1.0 ± 0.0h	–	bh	–
4-*O*-Methylgallic-3-*O*-sulfate	5-OH	4-OCH_3	3-*O*-s		275 ± 82d	2.1 ± 0.3d	d	d	–
Protocatechuic acid-3-*O*-glucuronide	4-OH	–	3-*O*-glc		11 ± 3a	2.7 ± 1.0a	abce	abce	abe
Protocatechuic acid-3-*O*-sulfate	4-OH	–	3-*O*-s		157 ± 116a*; 15.4 ± 8.2p	11.4 ± 3.8a*; 1.6 ± 0.9p	abcgep	abcep	abe
Protocatechuic acid-4-*O*-glucuronide	3-OH	–	4-*O*-glc		68 ± 61a	3.8 ± 0.8a	abcep	abce	abe
Protocatechuic acid-4-*O*-sulfate	3-OH	–	4-*O*-s		157 ± 116a*	11.4a ± 3.8*	abcgep	abce	abe
Syringic acid	4-OH	3,5-OCH_3	–		8 ± 6d; 777 ± 182h	0.3 ± 0.2d; 1.0 ± 0.0h	df	bcdh	–
Vanillic acid	4-OH	3-OCH_3	–		1845 ± 838a; 410 ± 115d; 379 ± 111h; 91.5 ± 38.4p	12.5 ± 11.5a; 1.8 ± 0.8d; 1.2 ± 0.5h; 1.4 ± 0.7p	b–gkmp	a–dhep	abe
Vanillic acid-4-*O*-glucuronide	–	3-OCH_3	4-*O*-glc		24 ± 4a	4.8 ± 0.4a	abceg	abceg	abe
Vanillic acid-4-*O*-sulfate	–	3-OCH_3	4-*O*-s		430 ± 299a*; 1054 ± 274d	30.1 ± 11.4a*; 2.1 ± 0.8d	a–eg	a–de	abe
Benzoic acid methyl esters									
Methyl-3,4-dihydroxybenzoate	3,4-OH	–	–		12 ± 5a; 1.8 ± 1.1p	8.4 ± 5.7a; 1.7 ± 1.4p	aegp	abcegp	abe
Methyl-4-hydroxybenzoate	4-OH	–	–		–	–	g	g	–
Methyl vanillate	4-OH	3-OCH_3	–		–	–	e	e	abe
Catechol derivatives									
Catechol	1,2-OH	–	–		–	–	p	–	–
Catechol-*O*-sulfate	1-OH	–	2-*O*-s		24555 ± 3775d	7.1 ± 0.4d	d	d	–
4-Methylcatechol-*O*-sulfate	1-OH	–	2-*O*-s, 4-CH_3		3497 ± 1192d	7.7 ± 3.2d	d	d	–

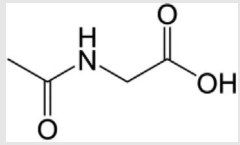
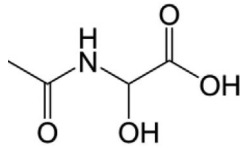
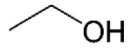
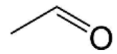
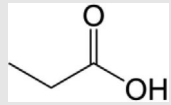
(Continues)

TABLE 3 (Continued)

Metabolite	Benzene ring substituents			Functional group in C1 of benzene	C_{max} (nM)	t_{max} (h)	Detected in:		
	OH	OCH_3	Others				Urine	Blood	Feces
Chlorogenic acid derivatives									
Chlorogenic acid	3,4-OH	–	–		5 ± 2d; 36.4 ± 24.0p	0.7 ± 0.3d; 2.5 ± 0.8p	dp	dp	–
Cinnamic acids and hydroxycinnamic acids									
Cinnamic acid	–	–	–		123 ± 34d	6.2 ± 2.4d	–	d	–
Caffeic acid	3,4-OH	–	–		1 ± 1d; 27.1 ± 18.9p	0.1 ± 0.1d; 1.7 ± 1.2p	dfgp	dlp	ab
Caffeic acid-3-*O*-glucuronide	4-OH	–	3-*O*-glc		16 ± 4d	1.1 ± 0.2d	d	d	–
Caffeic acid-4-*O*-glucuronide	3-OH	–	4-*O*-glc		59 ± 8d	1.2 ± 0.1d	d	d	–
Caffeic acid-3-*O*-sulfate	4-OH	–	3-*O*-s		–	–	kl	l	–
Caffeic acid-4-*O*-sulfate	3-OH	–	4-*O*-s		–	–	l	–	–
o-Coumaric acid	2-OH	–	–		6 ± 1d	1.2 ± 0.3d	d	d	–
m-Coumaric acid	3-OH	–	–		29 ± 14d	3.2 ± 0.8d	d	d	–
p-Coumaric acid	4-OH	–	–		131 ± 51d	1.0 ± 0.0d	bcdfglp	bdgl	b
p-Coumaric acid-4-*O*-glucuronide	–	–	4-*O*-glc		–	–	g	g	–
p-Coumaric acid-4-*O*-sulfate	–	–	4-*O*-s		–	–	g	–	–
Coumaric acid-*O*-sulfate	OH	–	*O*-s		–	–	l	–	–
Ferulic acid	4-OH	3-OCH_3	–		827 ± 371a; 47 ± 12d	8.2 ± 4.1a; 1.0 ± 0.0d	abcefgikp	a–egilp	abe
Ferulic acid-4-*O*-glucuronide	–	3-OCH_3	4-*O*-glc		165 ± 29d; 18 ± 2k	1.3 ± 0.2d; 1.5k**	dgk	dgk	–
Ferulic acid-4-*O*-sulfate	–	3-OCH_3	4-*O*-s		2268 ± 794d; 47 ± 14k	3.6 ± 2.6d; 1k**	dgkl	dkl	–
Isoferulic acid	3-OH	4-OCH_3	–		4592 ± 2251d	3.8 ± 2.5d	df	d	–
Isoferulic acid-3-*O*-glucuronide	–	4-OCH_3	3-*O*-glc		387 ± 95d; 14 ± 2k; 161 ± 130p	1.9 ± 0.6d; 1.5k**; 2.2 ± 1.2p	dklp	dkp	–
Isoferulic acid-3-*O*-sulfate	–	4-OCH_3	3-*O*-s		49 ± 6d	4.1 ± 2.5d	dkl	d	–
Sinapic acid	4-OH	3,5- OCH_3	–		46 ± 11d	1.9 ± 0.8d	bcdp	d	–

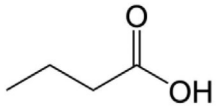
(Continues)

TABLE 3 (Continued)

Metabolite	Benzene ring substituents			Functional group in C1 of benzene	C_{max} (nM)	t_{max} (h)	Detected in:		
	OH	OCH_3	Others				Urine	Blood	Feces
Hippuric acid derivatives									
Hippuric acid	–	–	–		1962 ± 1389a; 42926 ± 12282d; 4649.2 ± 1293.3p	15.7 ± 4.1a; 21.8 ± 2.2d; 1.7 ± 1.6p	abdgijkp	abdgip	ab
2-Hydroxyhippuric acid	2-OH	–	–		7 ± 2d;	6.4 ± 3.3d;	d	d	–
3-Hydroxyhippuric acid	3-OH	–	–		45 ± 7d	8.3 ± 3.9d	dm	d	–
4-Hydroxyhippuric acid	4-OH	–	–		592 ± 157d; 78 ± 12k	3.8 ± 3.8d; 1k**	dkm	dk	–
3-Methylhippuric acid	–	–	$3\text{-}CH_3$		–	–	bp	–	–
4-Methylhippuric acid	–	–	$4\text{-}CH_3$		–	–	bp	–	–
α-Hydroxyhippuric acids									
α-Hydroxyhippuric acid	–	–	–		2943 ± 587d	3.9 ± 2.5d	d	d	–
Phenolic alcohols									
4-Hydroxybenzyl alcohol	4-OH	–	–		–	–	bc	–	–
Phenolic aldehydes									
3,4-Dihydroxybenzaldehyde	3,4-OH	–	–		34 ± 10d; 12.3 ± 6.5p	4.1 ± 2.6d; 1.1 ± 1.1p	adgp	bcdgp	ab
4-Hydroxybenzaldehyde	4-OH	–	–		667 ± 653a; 77 ± 18d; 264.2 ± 122.7p	5.6 ± 3.1a; 4.9 ± 2.5d; 1.2 ± 1.0p	adgp	a–dgp	ab
4-Methoxybenzaldehyde	–	$4\text{-}OCH_3$	–		–	–	–	–	a
Phloroglucinaldehyde	2,4,6-OH		–		582 ± 536a; 29 ± 8h; 13.3 ± 7.0p	2.8 ± 1.1a; 2.4 ± 0.9h ; 1.6 ± 1.3p	abcp	bcghp	ab
Phenylacetic acid derivatives									
Homoprotocatechuic acid	3,4-OH	–	–		476 ± 138d; 180 ± 89k	7.3 ± 2.3d; 6k**	a–gkp	dgk	abe

(Continues)

TABLE 3 (Continued)

Metabolite	Benzene ring substituents			Functional group in C1 of benzene	C_{max} (nM)	t_{max} (h)	Detected in:		
	OH	OCH_3	Others				Urine	Blood	Feces
Homovanillic acid	4-OH	3-OCH_3	–		511 ± 165d	5.6 ± 0.9d	bcdfgkmp	bdg	b
Homovanillic acid-4-*O*-sulfate	–	3-OCH_3	4-*O*-s		30 ± 10d	10.2 ± 3.5d	d	d	–
Homoisovanillic acid	3-OH	4-OCH_3	–		–	–	g	g	–
2-Hydroxyphenyl acetic acid	2-OH	–	–		–	–	g	g	–
3-Hydroxyphenyl acetic acid	3-OH	–	–		615 ± 360d	10.9 ± 3.4d	dfg	dg	–
4-Hydroxyphenyl acetic acid	4-OH	–	–		1849 ± 724d; 23.1 ± 17.0p	13.8 ± 4.0d; 1.3 ± 1.2p	adegp	dgp	ae
Phenylacetic acid	–	–	–		8304 ± 1886d	9.4d	d	d	–
Phenylpropanoic acid derivatives									
Dihydrocaffeic acid	3,4-OH	–	–		93 ± 32d	7.6 ± 3.3d	dflm	–	–
Dihydrocaffeic acid-3-*O*-glucuronide	4-OH	–	3-*O*-glc		84 ± 11d	22.2 ± 1.8d	dl	dl	–
Dihydrocaffeic acid-3-*O*-sulfate	4-OH	–	3-*O*-s		1656 ± 1116d	8.1 ± 3.1d	dgk	d	–
Dihydrocoumaric acid					–	–	l	l	–
Dihydrocoumaric acid-*O*-sulfate					–	–	l	l	–
Dihydro-*p*-coumaric acid	4-OH	–	–		–	–	i	i	–
Dihydroferulic acid	4-OH	3-OCH_3			304 ± 122d	6.1 ± 3.4d	dfjl	d	–
Dihydroferulic acid-4-*O*-glucuronide	–	3-OCH_3	4-*O*-glc		201 ± 59d	7.1 ± 3.3d	dg	d	–
Dihydroferulic acid-4-*O*-sulfate	–	3-OCH_3	4-*O*-s		197 ± 96d	6.8 ± 3.3d	dgl	dl	–
Dihydroisoferulic acid	3-OH	4-OCH_3	–		–	–	f	–	–
Dihydroisoferulic acid-3-*O*-glucuronide	–	4-OCH_3	3-*O*-glc		23 ± 10d	5.1 ± 2.5d	d	d	–
Dihydroisoferulic acid-3-*O*-sulfate	–	4-OCH_3	3-*O*-s		97 ± 42d	4.0 ± 2.5d	d	d	–

(Continues)

TABLE 3 (Continued)

Metabolite	Benzene ring substituents			Functional group in C1 of benzene	C_{max} (nM)	t_{max} (h)	Detected in:		
	OH	OCH_3	Others				Urine	Blood	Feces
3-Hydroxyphenylpropionic acid	3-OH	–	–		–	–	fg	g	–
3-Hydroxyphenylpropionic acid sulfate	3-OH	–	–		–	–	g	–	–
Pyrogallol derivatives									
1-Methylpyrogallol-*O*-sulfate	diOH	1-OCH_3	*O*-s		538 ± 172d	9.1 ± 3.8d	d	d	–
2-Methylpyrogallol-*O*-sulfate	diOH	2-OCH_3	*O*-s		185 ± 44d	5.3 ± 2.6d	d	d	–
Phloroglucinol	1,3,5-OH	–	–		–	–	gp	–	–
Pyrogallol-1-*O*-sulfate	2,3-OH	–	1-*O*-s		199 ± 79d	8.7 ± 3.1d	d	d	–
Pyrogallol-2-*O*-sulfate	1,3-OH	–	2-*O*-s		339 ± 123d	6.2 ± 2.3d	d	d	–

Note: The metabolites consist of a substituted benzene ring, and the substituents and the functional group in C-1 are given in the table. Abbreviation s means a sulfate and glc a glucuronide.

The referred studies were mainly conducted with berry meals rich in nonacylated anthocyanins except for: pure ^{13}C-traced cyanidin-3-O-glucoside was consumed in studies **a** (de Ferrars, Czank, Zhang, et al., 2014) and **e** (Czank et al., 2013); acylated anthocyanins were consumed in study **j** (Tsang et al., 2015) (purple potatoes), studies **l** (Stalmach et al., 2011) and **m** (Stalmach et al., 2013) (grape juice containing both nonacylated and acylated anthocyanins), and study **p** (Jokioja et al., 2021) (purple potato extract).

LC-MS was used to identify and quantify the metabolites except for the study **m** in which GC-MS was used (Stalmach et al., 2013).

The C_{max} and t_{max} values refer to plasma samples.

*t_{max} includes isomers due to analytical challenges related to chromatographic separation.

**deviation not reported.

Literature reference and the study meal given:

a, $n = 8$, 500 mg of ^{13}C-labeled cyanidin-3-*O*-glucoside, errors are given as standard error of the mean (SEM) (de Ferrars, Czank, Zhang, et al., 2014).

b, $n = 15$, 500 mg of elderberry anthocyanins (de Ferrars, Czank, Saha, et al., 2014).

c, $n = 52$, 500 mg of elderberry anthocyanins (de Ferrars, Cassidy, et al., 2014).

d, $n = 10$, cranberry juice containing 787 mg of polyphenols of which 16.2 mg are anthocyanins (Feliciano et al., 2016).

e, $n = 8$, 500 mg of ^{13}C-labeled cyanidin-3-*O*-glucoside (Czank et al., 2013).

f, $n = 6$, bilberry and lingonberry puree containing 500 mg of anthocyanins (Nurmi et al., 2009).

g, $n = 2$, 125 g of raspberries containing 71 mg of anthocyanins (Zhang et al., 2018).

h, $n = 5$, 150 g bilberries containing 2.5 g of anthocyanins (Mueller et al., 2017).

i, $n = 6$, 500 mg of aronia berry extract containing 45.1 mg of anthocyanins (Xie et al., 2016).

j, $n = 5$, 400 g of purple potatoes, amount of anthocyanins unknown (Tsang et al., 2015).

k, $n = 9$, 300 g of blended raspberries, containing 553 μmol of polyphenols, of which 53% anthocyanins (292 μmol), 45% ellagic acid conjugates, 2% phenolic acids), and errors are given as standard errors (SE) (Ludwig et al., 2015).

l, n = 8, 350 ml of 100% grape juice containing 528 μmol of polyphenols, of which 46% were anthocyanins, and of which 40% were petunidin derivatives acylated to acetic acid or *p*-coumaric acid (Stalmach et al., 2011).

m, $n = 8$, 350 ml of grape juice containing 528 μmol polyphenols of which 46% was partly acylated anthocyanins (Stalmach et al., 2013).

n, $n = 10$, 330 ml of grape/blueberry juice containing 278 mg of anthocyanins of which 55 mg were monoacylated (acetic acid and/or *p*-coumaric acid) malvidin, peonidin, petunidin, cyanidin, and delphinidin glucosides (Kuntz et al., 2015).

o, $n = 10$, 330 ml of grape/blueberry smoothie containing 324 mg of anthocyanins of which 46 mg were monoacylated (acetic acid and/or *p*-coumaric acid) malvidin, peonidin, petunidin, cyanidin, and delphinidin glucosides (Kuntz et al., 2015).

p, $n = 17$, 30 ml of purple potato extract mixed with 350 g of yellow potatoes, the extract contained 152 mg of 99% acylated anthocyanins and 140 mg of hydroxycinnamic acid derivatives (Jokioja et al., 2021).

6 | EFFECT ON POSTPRANDIAL GLYCEMIA AND INSULINEMIA

6.1 | Acylated anthocyanins

6.1.1 | Clinical trials

As there are currently no clinical investigations reporting the effect of purified acylated anthocyanins on postprandial blood glucose and insulin, only animal studies are reviewed.

6.1.2 | Animal trials

One dose of peonidin-3-*O*-[2-*O*-(6-*O*-feruloyl-glucoside)-6-*O*-caffeoyl-glucoside]-5-*O*-glucoside extracted from purple sweet potatoes (100 mg/kg) to the stomach decreased the area under the glucose curve (AUC) until 120 min and postprandial blood glucose and insulin at 30 and 60 min in normoglycemic Sprague–Dawley rats ($n = 4$) when fed with maltose (2 g/kg) but not with sucrose or glucose (Matsui et al., 2002). When hyperglycemic C57BL/6 mice ($n = 5$) were given one dose (80 mg/kg) of diacylated cyanidin-3-caffeoyl-*p*-hydroxybenzoylsophoroside-5-glucoside or peonidin-3-(6′′-caffeoyl-6′′′-feruloylsophoroside)-5-glucoside extracted from purple sweet potatoes, the cyanidin derivative decreased the blood glucose 1 and 2 h postprandially and peonidin derivative had a corresponding effect 1 h postprandially. Insulin was not analyzed (Jang et al., 2019). Results of the studies, summarized in Table 4, indicate that acylated anthocyanins affect the postprandial glycemia beneficially. The potential mechanisms are discussed in Section 8.

However, anthocyanins are rarely ingested as such and investigations of pure compounds do not provide information about the possible effects of other compounds and matrix of food, and thus the extracts and whole foods rich in acylated anthocyanins are discussed next.

6.2 | Extracts rich in acylated anthocyanins

6.2.1 | Clinical trials

In a cross-over clinical trial, 17 healthy males consumed purple potato extract (cultivar Synkeä Sakari, 152 mg of anthocyanins and 140 mg of other phenolic compounds) mixed with yellow potatoes or yellow potatoes as control. The extract decreased the highest rise of both postprandial glucose and insulin, and thereafter decreased the glucose from declining below fasting state. The incremental areas under the curves (iAUC) until 120 min of glucose and insulin were lower after the extract (Jokioja et al., 2020).

6.2.2 | Animal studies

After feeding purple sweet potato extract (700 mg/kg/day of anthocyanins [90%] and other flavonoids) to mice for 20 weeks with HFD, the fasting state glucose levels decreased, and glucose tolerance and insulin resistance improved as analyzed with an oral glucose tolerance test (OGTT) and intraperitoneal insulin tolerance test (ipITT) (Zhang et al., 2013). A lyophilized extract (14 mg/g of anthocyanins) from red cabbage was fed daily for 4 weeks to diabetic rats (800 mg/kg body weight), resulting in decreased fasting state glucose, glycated hemoglobin (HbA1c), and OGTT (Buko et al., 2018). An acute dose of anthocyanin-rich extract (1 ml, 400 mg/kg) from purple sweet potatoes administered to the stomachs of normoglycemic rats decreased postprandial glucose when ingested maltose, but not with sucrose or glucose (1 ml, 2 g/kg) (Matsui et al., 2002). A lyophilized extract from purple sweet potato (932.5 mg/g of total flavonoids) was fed (10 g/kg body weight) to diabetic mice for a month; the extract decreased the fasting state glucose (Zhao et al., 2013). However, when an anthocyanin-containing extract from water yam was fed to hyperglycemic rats daily for 4 weeks, only insignificant decreasing trend of the fasting state plasma glucose was detected weekly (Estiasih et al., 2018).

A purple potato extract rich in acylated anthocyanins (cultivar Blue Congo, 72.7 mg/g DW of anthocyanins) and phenolic acids (167.4 mg/g DW, caffeoylquinic acid derivatives) fed to diabetic rats for 2 weeks showed statistically insignificant decrease of fasting state glucose and significant decrease of glycated hemoglobin compared to the diabetic rats not fed with the extract. Insulin was not measured (Strugała et al., 2019). When extracts rich in protein-bound or free anthocyanins of purple potatoes were fed daily for 7 weeks to diabetic mice with HFD, both fasting state glucose and glucose tolerance improved, while that of insulin did not (Jiang et al., 2020). There were no effect on the fasting state glucose and insulin after feeding diabetic rats daily for 8 weeks with HFD supplemented with 25 or 50 mg/kg body weight of lyophilized purple potato extract (Synkeä Sakari, 248.74 mg/g DW) (Chen et al., 2020).

However, even though anthocyanin-rich extracts are easily produced from various food sources, they usually also contain other compounds than anthocyanins.

TABLE 4 Effect of acylated anthocyanins, anthocyanin extracts, and foods rich in acylated anthocyanins on the fasting state (fs) and postprandial (pp) glycemia of rodents and human volunteers

Food origin	*n*	Study design	Study duration	Control meal/diet	Effect on blood glucose and insulin	References
Clinical trials						
Extracts						
Purple potato extract added to yellow potatoes	17	Cross-over, healthy volunteers	Acute	Yellow potatoes without the extract	↓ Pp glucose at 20 and 40 min ↑ Pp glucose at 180 and 240 min ↓ Pp insulin at 20, 40, and 60 min ↑ Pp insulin at 180 and 240 min ↓ Pp glucose iAUC120 ↓ Pp insulin iAUC120	Jokioja et al. (2020)
Whole foods						
Purple potato (steam-cooked, mashed)	13	Cross-over, healthy volunteers	Acute	Yellow potatoes (steam-cooked, mashed)	↓ Pp glucose at 40 min ↓ Pp insulin iAUC120 and 240 min	Linderborg et al. (2016)
Purple and red potato (chips)	11	Cross-over, healthy volunteers	Acute	Salted wheat crackers or white potato chips	↓ Pp glucose compared to crackers Nonsignificant, decreasing trend of total AUC120 min and iAUC30–60 min compared to other chips Delayed glucose peak time of both chips	Moser et al. (2018)
Purple and red potatoes (oven-baked)	9	Cross-over, healthy volunteers	Acute	Glucose or white potatoes or yellow potatoes	↓ Pp glucose at 15 min - all potato types versus control glucose ↓ Pp glucose at 120 min after red potato meal versus control glucose No difference in pp insulin No difference in AUC120 min of glucose or insulin	Ramdath et al. (2014)
Purple potatoes (microwave-cooked)	18	Cross-over, hypertensive, overweight, or obese volunteers	Twice daily, 4 weeks	Potato-free diet	No difference in fs glucose No difference in HbA1c	Vinson et al. (2012)
Animal studies						
Purified anthocyanins						
Purple sweet potato (purified anthocyanin[a])	4	Normoglycemic rats	Acute, stomach sonde	Maltose, sucrose, or glucose without anthocyanins	↓ Pp glucose and insulin after maltose intake at 30 and 60 min ↓ AUC120 min No difference in pp glucose or insulin after the intake of sucrose and glucose	Matsui et al. (2002)

(Continues)

TABLE 4 (Continued)

Food origin	*n*	Study design	Study duration	Control meal/diet	Effect on blood glucose and insulin	References
Purple sweet potato (purified anthocyanin[b])	5	Hyperglycemic mice	Acute, oral	Distilled water	↓ Pp glucose at 1 and 2 h	Jang et al. (2019)
Purple sweet potato (purified anthocyanin[c])	5	Hyperglycemic mice	Acute, oral	Distilled water	↓ Pp glucose at 1 h	Jang et al. (2019)
Extracts						
Purple sweet potato (anthocyanin extract)	4	Normoglycemic rats	Acute, stomach sonde	Maltose, sucrose, or glucose without anthocyanins	↓ Pp glucose after maltose intake at 30 min and insulin at 30 and 60 min No difference in pp glucose after the intake of sucrose and glucose	Matsui et al. (2002)
Purple sweet potato (extract)	10	Normoglycemic mice	Daily for 20 weeks	High-fat diet (HFD)	↓ Fs glucose ↓ Pp glucose levels at 0, 15, 30, 60, 90, and 120 min during OGTT ↓ Glucose levels at 0, 15, 30, 60, 90, and 120 min during ipIGTT	Zhang et al. (2013)
Water yam (extract)	5	Hyperglycemic rats	Daily for 4 weeks, oral	Baseline diet	Insignificant decreasing trend of fs glucose each week 1–4	Estiasih et al. (2018)
Red cabbage[e] (lyophilized extract)	8	Diabetic rats	Daily for 4 weeks, intragastric administration	Baseline diet + saline	↓ Fs glucose ↓ HbA1c ↓ Glucose during OGTT (AUC60 min)	Buko et al. (2018)
Purple potato (lyophilized extract)	8	Diabetic rats	Daily for 8 weeks	Baseline high-fat diet	No difference in fs glucose No difference in fs insulin	Chen et al. (2020)
Purple potato (extract of protein-bound anthocyanins)[h]	6	Diabetic mice	Daily for 7 weeks	Baseline high-fat diet	↓ Fs glucose at every week (w1–7) ↑ Glucose tolerance iAUC120 min (OGTT); no difference on glucose at time points No difference in fs insulin after the study	Jiang et al. (2020)
Purple potato (extract of free anthocyanins)	6	Diabetic mice	Daily for 7 weeks	Baseline high-fat diet	↓ Fs glucose at every week (w1–7) ↑ Glucose tolerance iAUC120 min (OGTT); no difference on glucose at time points No difference in fs insulin after the study	Jiang et al. (2020)

(Continues)

TABLE 4 (Continued)

Food origin	*n*	Study design	Study duration	Control meal/diet	Effect on blood glucose and insulin	References
Purple potato[d] (dried phenolic extract)	8	Diabetic rats	Daily for 2 weeks, oral	Baseline diet	Insignificant decreasing trend of fs glucose ↓ HbA1c	Strugała et al. (2019)
Purple sweet potato extract (lyophilized)	10	Diabetic mice	Daily for 5 weeks, oral	Baseline diet	↓ Fs glucose	Zhao et al. (2013)
Whole foods						
Purple potatoes (freeze-dried, baked)	15	Obese rats	Daily for 8 weeks, oral	High-fat baseline diet or high-fat baseline diet + white potatoes (WP)	↓ Pp glucose at 60, 90, and 120 min during ipGTT compared to WP and HFD ↓ Pp glucose at 45 min during ipITT compared to HFD ↓ Purple potatoes and WP decreased fs insulin ↑ Insulin sensitivity compared to HFD	Ayoub et al. (2017)
Purple carrots (raw)	15	Obese rats	Daily for 8 weeks, oral	Baseline diet and baseline diet + orange carrots	No difference in glucose Insignificant decreasing trend of fs insulin after purple carrots compared with orange ones and baseline	Ayoub et al. (2017)
Red lettuce[f] (lyophilized leaf powder)	8	Obese, insulin-resistant hyper-glycemic mice	Daily for 8 days, intragastric	Baseline diet + vehicle (water)	↓ Pp glucose measured 6 h after administration on the sixth treatment day ↓ Pp glucose at 30 min during OGTT after 7 treatment days Improved insulin response in insulin tolerance test	Cheng et al. (2014)
Concord grape (freeze-dried powder)	8	Obese rats	Daily for 12 weeks, oral	Baseline diet	No difference in fs glucose No difference in glucose during OGTT or ipGTT	Overall et al. (2017)
Purple potato (lyophilized powder)	8	Diabetic rats	Daily for 7 weeks, oral	Baseline diet	↓ Fs glucose at w3, no effect at w5 and w7 ↑ Fs insulin	Choi et al. (2013)
Purple carrot (pasteurized juice)	12	Diabetic mice	Daily for 8 weeks, oral	Baseline diet	↓ Glucose during OGTT (AUC120 min)	Poudyal et al. (2010)

Note: In clinical trials, *n* represents the total number of volunteers. In animal studies, *n* represents the number of animals per group.
ANC, anthocyanin; AUC, area under curve; HbA1c, glycated hemoglobin; ipITT, intraperitoneal insulin tolerance test; ipGTT, intraperitoneal glucose tolerance test; NA, not available; OGTT, oral glucose tolerance test; pp, postprandial; fs, fasting state.
Main reported anthocyanins in the foods:
a, peonidin-3-*O*-[2-*O*-(6-*O*-feruloyl-glucopyranosyl)-6-*O*-caffeoyl-glucopyranoside]-5-*O*-glucopyranoside.
b, cyanidin-3-caffeoyl-p-hydroxybenzoylsophoroside-5-glucoside.
c, peonidin-3-(6′′-caffeoyl-6′′′-feruloylsophoroside)-5-glucoside.
d, petunidin-3-*O*-*p*-coumaroyl-rutinoside-5-*O*-glucoside.
e, delphinidin-3-rutinoside-5-hexoside + cyanidin-3-caffeoylferuloylsophoroside-5-glucoside + delphinidin-3-feruloyl-rhamnosyl-hexoside.
f, cyanidin-3-malonyl-glucoside.
g, delphinidin- and cyanidin-3-*O*-glucosides, delphinidin-3,5-*O*-(coumaroyl)-diglucoside.
h, anthocyanins not identified.
i, cyanidin-3-sophoroside-5-glucoside, cyanidin-3-sophoroside-5-glucoside.

6.3 | Foods rich in acylated anthocyanins

6.3.1 | Clinical trials

An acute dose (50 g of available carbohydrates, 290−380 g of potato) of oven-baked purple (cultivar Purple Majesty) and red potatoes (cultivar Y38), with 16 and 15 mg/100 g DW of anthocyanins, decreased the postprandial glucose of healthy volunteers ($n = 9$) 15 min after the intake compared to a control dose of glucose which had no effect on AUC120 min or insulin (Ramdath et al., 2014). Another study in which healthy volunteers ($n = 13$) consumed a meal of 350 g steam-cooked and mashed purple potatoes (140 mg of anthocyanins and 71 g of available carbohydrates) showed that purple potatoes decrease postprandial blood glucose at 40 min and iAUC of insulin (120 and 240 min) (Linderborg et al., 2016). A long-term study conducted with hypertensive and overweight/obese volunteers showed that 138 g of microwave-cooked purple potatoes (Purple Majesty) containing 276 mg of phenolic compounds per meal and 6.5 mg/g DW anthocyanins twice daily for 4 weeks did not alter fasting state glycemia or glycated hemoglobin (HbA1c) (Vinson et al., 2012). An acute intake of purple potato chips providing 50 g of available carbohydrates and 1.05 mg of anthocyanins caused a non-significant decreasing trend in the postprandial glucose (AUC120min and AUC30−60min) compared with the red (3.1 mg of anthocyanins) and white potato chips. Both red and purple chips delayed the peak glucose concentration. Insulin was not measured (Moser et al., 2018).

6.3.2 | Animal studies

Pasteurized purple carrot juice was given to diabetic mice daily for 8 weeks with maize starch or high-carbohydrate and HFD containing 24.4 or 15.2 mg/kg of anthocyanins, resulting in improved glucose tolerance. The effect was hypothesized to be affected by the carrot anthocyanins, as the amount of β-carotene in the juice was negligible (Poudyal et al., 2010). An 8-day daily oral administration of lyophilized Rutgers scarlet lettuce (*Lactuca sativa* L., 100 and 300 mg/kg) to hyperglycemic, obese mice leads to reduced hyperglycemia and improved insulin sensitivity. The main compounds in the lettuce were chlorogenic acid (27.6 mg/g DW), cyanidin-malonyl-glucoside (20.5 mg/g DW), and quercetin-malonyl-glucoside (35.7 mg/g DW) (Cheng et al., 2014). However, feeding obese rats daily for 12 weeks with freeze-dried Concord grape powder (400 μg/g anthocyanins) did not affect fasting state glucose nor oral glucose tolerance (Overall et al., 2017) Also, HFD supplemented with raw, freeze-dried purple (3.35 mg/g DW anthocyanins) or orange carrots (300 g/kg diet) daily for 8 weeks did not affect blood glucose at separate time points nor AUC measured with intraperitoneal glucose tolerance test and ipITT in obese rats (Ayoub et al., 2017).

When lyophilized purple potatoes (Bora Valley) were fed daily (0%, 10%, or 20% of the baseline diet) for 7 weeks to diabetic rats ($n = 8$ per group), the powder decreased fasting state glucose in the 10% and 20% groups at the third week when compared to the diabetic control group. The fasting state insulin increased in the group fed with 20% of purple potatoes compared to the control group (Choi et al., 2013). Baked and freeze-dried purple potatoes (450 g/kg of diet, 1.47 mg/g DW of anthocyanins) or white potatoes (450 g/kg of diet) were fed to obese rats ($n = 15$ per group) for 8 weeks with HFD, and the results were compared to a control group fed with the HFD without potatoes. The long-term supplementation of purple potatoes decreased the blood glucose levels 60, 90, and 120 min after the glucose tolerance test when compared to the control and white potato groups. Fasting state insulin was significantly lower in groups fed with potatoes compared to the control. Also, ipITT and homeostatic model assessment of insulin resistance (HOMA-IR) supported enhanced insulin sensitivity in the purple potato group compared to the control group (Ayoub et al., 2017).

Also, other compounds than anthocyanins may have affected the perceived health effects when studying whole foods, but using whole foods provides information about the antagonistic effects of other compounds and food matrix.

7 | EFFECT ON POSTPRANDIAL INFLAMMATION

7.1 | Overview of diet-related oxidative stress and inflammation

Consuming glucose or fat evokes an acute, short-timed immune response mediated by the innate immunity system linked with oxidative stress (Calder et al., 2009, 2011; Hansen et al., 1997; Meessen et al., 2019; Muñoz & Costa, 2013). One meal high in carbohydrates or fat causes an inflammatory response in healthy normoglycemic volunteers, carbohydrates having more severe effect than fat (Gregersen et al., 2012). The inflammatory response worsens with higher glycemic index (Dickinson et al., 2008). The acute postprandial inflammation is usually resolved quickly, but failure of resolvation leads to chronic inflammation (Calder et al., 2009; Muñoz & Costa, 2013). Chronic inflammation ultimately impairs the function of the insulin-secreting pancreatic β-cells, which further promotes the formation of obesity, insulin resistance, and type

2 diabetes (Bloch-Damti & Bashan, 2005; Evans et al., 2002; Wellen & Hotamisligil, 2005).

Oxidative stress is evoked when excessive flux of nutrients in the mitochondria overloads the mechanism for glucose decomposition in muscle and adipose tissues. The overloaded tricarboxylic acid cycle produces excess amounts of nicotinamide adenine dinucleotide, all of which may not be reduced. The electrons are transferred to oxygen, which leads to the formation of superoxide anion and other free radicals, nitrogen oxide, and peroxynitrite (Ceriello & Motz, 2004). Meal-induced oxidative stress alters the insulin-dependent signaling pathways (Bloch-Damti & Bashan, 2005) and nuclear factor κB (NF-κB) (Dhindsa et al., 2004; Patel et al., 2007), which leads to the secretion of cytokines, such as interleukin-6 (IL-6) and the tumor necrosis factor α (TNF-α) (Barnes, 1997; Gregersen et al., 2012). Oxidative stress is prolonged in obesity compared to a healthy state (Patel et al., 2007) and high, repetitive postprandial glucose fluctuations cause more oxidative stress in both healthy and diabetic volunteers than chronically elevated blood glucose (Ceriello et al., 2008; Monnier et al., 2006). Improving antioxidant defense mechanisms prevents oxidative stress and decreases postprandial inflammation; dietary antioxidants include, for example, carotenoids, vitamins E and C and polyphenolic compounds, such as flavonoids (Calder et al., 2009).

7.2 | Foods rich in acylated anthocyanins

7.2.1 | Clinical trials

Acute intake of purple potato extract mixed with yellow potatoes (350 g) affected some of the studied 92 inflammation biomarkers in healthy men ($n = 17$) when compared to a meal of yellow potatoes. The proinflammatory cytokine IL-6, which is usually increased after a high-carbohydrate meal, had statistically insignificant trend of decrease after the study meal. FGF-19, which may have antidiabetic properties, was elevated after the study meal, but CCL20 was increased (Jokioja et al., 2020). In a long-term parallel study, daily consumption of white, yellow, or purple potatoes (150 g) for 6 weeks reduced the proinflammatory marker, fasting state C-reactive protein, in the purple potato group compared to the white potato group, whereas IL-6 was reduced by both red and purple potato treatments in comparison with the white potatoes in healthy volunteers ($n = 12$) (Kaspar et al., 2011). Another long-term trial in which overweight men ($n = 16$) consumed dried purple carrot powder corresponding to 300 g of fresh carrots providing 118.5 mg anthocyanins and 259.2 mg phenolic acids daily for 4 weeks did not alter inflammation biomarkers in comparison to the same amount of dried orange carrot (Wright et al., 2013).

7.2.2 | *In vitro* studies

A semipurified purple potato extract rich in petunidin-3-*O*-*p*-coumaroylrutinoside-5-*O*-glucoside and a purple carrot extract added to TNF-α stimulated Caco-2 cell monolayer decreased IL-8 levels *in vitro*. In a coculture with Caco-2 BBe1 cells, the absorbed purple carrot and purple potato anthocyanins inhibited the expression of TNF-α and IL-8 in the lipopolysaccharide-induced macrophages (THP-1) both at protein and gene levels, but the purple potato was more efficient (Zhang et al., 2017). Another *in vitro* study showed that the phenolic extracts of purple potatoes and purple carrots decreased the hydrogen peroxide-induced interleukins IL-1β, IL-6, IL-8, and TNF-α in Caco-2 cells (Zhang, Liu, et al., 2016). Moreover, purple carrot extract applied to a coculture of Caco-2 cells and lipopolysaccharide-induced RAW 264.7 macrophage cells downregulated the mRNA expression of IL-1β and IL-6 (Olejnik et al., 2016). In lipopolysaccharide-induced RAW 264.7 macrophage cells, crude anthocyanin extracts from purple sweet potatoes decreased TNF-α and IL-6 (Sugata, 2015).

8 | MOLECULAR MECHANISMS

The possible molecular mechanisms behind the glycemia and inflammation lowering effects of anthocyanins are reviewed next; the ones related to acylated anthocyanins are summarized in Table 5.

8.1 | Inhibition of digestive enzymes

Several *in vitro* studies indicate that anthocyanins inhibit structure-dependently the enzymes digesting carbohydrates as their inhibitory activities (IC_{50}) were within micromolar range. Starting from the human salivary α-amylase, it was inhibited *in vitro* by nonacylated cyanidin-3-glucoside, followed by cyanidin > delphinidin > delphinidin-3-glucoside > malvidin > cyanidin-3-arabinoside. The phenolic metabolites inhibited human salivary α-amylase even more than the hydroxysubstituted nonacylated anthocyanins (4-hydroxybenzaldehyde > gallic acid > protocatechuic aldehyde > ferulic acid > protocatechuic acid > syringic acid > vanillic acid) (Barik et al., 2020).

TABLE 5 A summary of the possible underlying molecular mechanisms behind the physiological effects of acylated anthocyanins

Molecular mechanism	Model food	Food origin	Study design	References
Inhibition of digestive enzymes				
Isolated acylated anthocyanins				
↓ Pancreatic α-amylase	Isolated mix of mainly acylated anthocyanins	Black carrot	*in vitro*	Kaeswurm et al. (2020)
↓ Intestinal α-glucosidase (maltase)	Isolated acylated anthocyanins	Purple sweet potato	*in vitro*	Matsui et al. (2001)
—Intestinal α-glucosidase (sucrase)	Isolated acylated anthocyanins	Purple sweet potato	*in vitro*	Matsui et al. (2001)
Extracts				
↓ α-Glucosidase	Anthocyanin fraction	Black carrot	*in vitro*	Esatbeyoglu et al. (2016)
↓ Pancreatic α-amylase	Extract rich in acylated and nonacylated anthocyanins	Purple maize	*in vitro*	Zhang et al. (2019)
↓ Pancreatic α-amylase	Extract	Red and purple potato	*in vitro*	Kalita et al. (2018)
— Pancreatic α-amylase	Extract	Red and purple potato	*in vitro*	Moser et al. (2018)
↓ Intestinal α-glucosidase	Extract	Purple potato	*in vitro*	Kalita et al. (2018)
↓ Intestinal α-glucosidase	Extract	Purple potato	*in vitro*	Moser et al. (2018)
↓ α-Glucosidase	Anthocyanin fraction	Purple sweet potato	*in vitro*	Esatbeyoglu et al. (2017)
Inhibition of the intestinal absorption of glucose				
Extracts				
↓ Glucose uptake	Extract	Purple carrot	*in vitro*	Zhang et al. (2017)
— Glucose uptake	Anthocyanin fraction	Purple carrot	*in vitro*	Esatbeyoglu et al. (2016)
↓ Glucose uptake	Extract	Purple potato	*in vitro*	Zhang et al. (2017)
↓ Glucose uptake	Extract	Purple potato	*in vitro*	Moser et al. (2018)
Increased uptake of glucose into muscle and adipose tissues				
Extracts				
↑ Restored glucose uptake in insulin resistance	Extract rich in acylated and nonacylated anthocyanins	Purple maize	*in vitro*	Zhang et al. (2019)
↑ Enhanced hepatic insulin signaling pathway (IRS-1/Pi3K/Akt)	Extract	Purple sweet potato	Animal study (mice fed for 20 weeks with HFD and extract)	Zhang et al. (2013)
Inhibition of hepatic glucose production (gluconeogenesis)				
Isolated acylated anthocyanins				
↓ The gene expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase	Isolated anthocyanins	Purple sweet potato	Animal study (diabetic mice fed daily for 7 weeks with HFD and anthocyanins)	Jiang et al. (2020)
↓ Glucose production	Isolated acylated anthocyanins	Purple sweet potato	*in vitro*	Jang et al. (2019)

(Continues)

TABLE 5 (Continued)

Molecular mechanism	Model food	Food origin	Study design	References
— Glucose production	Isolated acylated anthocyanin	Red lettuce	*in vitro*	Cheng et al. (2014)
Extracts				
↓ Hepatic mRNA level of the *G6PC* and *TBC1D1* genes	Extract	Purple potato	Animal study (diabetic mice fed daily for 8 weeks with extract)	Chen et al. (2020)
— *Gpx4* and *GSS* encoding glutathione peroxidase 4 and glutathione synthetase in hepatic HepG2 cells	Anthocyanin-rich fraction	Purple sweet potato	*in vitro*	Esatbeyoglu et al. (2017)
↓ Glucose production	Phenolic extract	Red lettuce	*in vitro*	Cheng et al. (2014)
Enhancing secretion of insulin via increased incretin secretion				
Extracts				
— GLP-1 secretion in the endoenterocrine GLUTag cells	Anthocyanin fraction	Black carrot	*in vitro*	Esatbeyoglu et al. (2016)
Decreased production of proinflammatory adipocytokines in adipocytes				
Extracts				
↓ Leptin	Extract	Purple sweet potato	*in vitro*	Ju et al. (2011)
Radical scavenging activity				
Isolated acylated anthocyanins				
Radical scavenger	Isolated acylated anthocyanin	Black carrot, red cabbage and purple sweet potato	*in vitro* (chemical antioxidant activity assay)	Stintzing et al. (2002)
Radical scavenger	Pure acylated anthocyanin	Commercial standard	*in vitro* (chemical antioxidant activity assay)	Kähkönen and Heinonen (2003)
Radical scavenger	Isolated anthocyanins	Eggplant	*in vitro* (chemical antioxidant activity assay)	Azuma et al. (2008)
Radical scavenger	Isolated acylated anthocyanin	Muscat Bailey A grape	*in vitro* (chemical antioxidant activity assay)	Tamura and Yamagami (1994)
Radical scavenger	Isolated diacylated anthocyanins	Purple sweet potato	*in vitro* (chemical antioxidant activity assay)	Jang et al. (2019)
Radical scavenger	Isolated acylated anthocyanins	Purple sweet potato	*in vitro* (chemical antioxidant activity assay)	Luo et al. (2018)
Radical scavenger	Isolated acylated anthocyanins	Red cabbage	*in vitro* (chemical antioxidant activity assay)	Wiczkowski et al. (2013)
Extracts				
↓ Hepatic reactive oxygen species (ROS)	Extract	Purple sweet potato	Animal study (mice fed with extract and HFD for 20 weeks)	Zhang et al. (2013)

(Continues)

TABLE 5 (Continued)

Molecular mechanism	Model food	Food origin	Study design	References
Radical scavenger	Extract	Purple carrot	*in vitro* (cellular antioxidant activity assay, Caco-2 cells)	Zhang et al. (2016)
Radical scavenger	Simulated digest of anthocyanin-rich extract	Purple potato	*in vitro* (chemical antioxidant activity assay after gastrointestinal model)	Ombra et al. (2015)
Radical scavenger	Extract	Purple potato	*in vitro* (cellular antioxidant activity assay, Caco-2 cells)	Zhang et al. (2016)
Radical scavenger	Extract	Purple sweet potato	*in vitro* (chemical antioxidant activity assay)	Ju et al. (2011)
Radical scavenger	Simulated digest of polyphenolic extract	Purple tomato	*in vitro* (chemical and cellular antioxidant activity assay (MCF-10A cells) after gastrointestinal digestion model)	Li et al. (2014)
Whole foods				
— Plasma antioxidant capacity	Acute meal	Purple potato	Clinical trial (healthy volunteers)	Moser et al. (2018)
— Plasma antioxidant capacity	Acute meal	Purple potato	Clinical trial (healthy volunteers)	Ramdath et al. (2014)
↑ Plasma antioxidant capacity	Acute meal	Purple potato	Clinical trial (healthy, overweight and obese volunteers)	Vinson et al. (2012)
Radical scavenger	Flour	Pigmented potato	*in vitro* (chemical antioxidant activity assay)	Nemś et al. (2015)
Radical scavenger	Snack	Pigmented potato	*in vitro* (chemical antioxidant activity assay)	Nemś et al. (2015); Nemś and Pęksa (2018)
Enhanced endogenous antioxidant defense				
Extracts				
↑ SOD, CAT, GPx, GSH	Phenolic extract	Purple potato	Animal study (diabetic rats, fed for 14 days)	Strugała et al. (2019)
↑ SOD, GPx	Anthocyanin extract	Purple sweet potato	Animal study (diabetic mice)	Jiang et al. (2020)
↑ GPx, GSH, SOD	Extract	Purple sweet potato	Animal study (mice fed with HFD and extract for 20 weeks)	Zhang et al. (2013)
↑ GPx, CAT	Phenolic extract (lyophilized)	Red cabbage	Animal study (diabetic rats, intragastric supplementation for 4 weeks)	Buko et al. (2018)
↓ COX-2, iNOS	Anthocyanin extract	Purple carrot	*in vitro*	Olejnik et al. (2016)
↑ CAT, GPx, SOD, GR	Extract	Purple carrot	*in vitro*	Zhang et al. (2016)
↑ CAT, GPx, SOD, GR	Extract	Purple potato	*in vitro*	Zhang et al. (2016)

(Continues)

TABLE 5 (Continued)

Molecular mechanism	Model food	Food origin	Study design	References
— Nrf2 and heme oxygenase 1	Anthocyanin-rich fraction	Purple sweet potato	*in vitro*	Esatbeyoglu et al. (2017)
↓ COX-2	Phenolic extract	Purple sweet potato	*in vitro*	Ju et al. (2011)
Whole foods				
↑ SOD, GPx	Flakes	Purple potato	Animal study (rats fed with flakes for 4 weeks)	Han et al. (2006)
Inhibition of the MAPK pathway				
Extracts				
↓ p-IκB kinase ↓ p-JNK1	Extract	Purple sweet potato	Animal study (mice fed for 20 weeks with HFD and extract)	Zhang et al. (2013)
↓ p-IκB kinase ↓ p-JNK	Extract	Purple potato	*in vitro*	Zhang et al. (2017)

—, no effect. HFD, high-fat diet.

Pancreatic α-amylase was inhibited by nonacylated cyanidin-3-sambubioside (Iwai et al., 2006), cyanidin, and cyanidin-3-glucoside but not by cyanidin-3-galactoside or cyanidin-3,5-diglucoside (Akkarachiyasit et al., 2010). Comparison of different anthocyanin glucosides shows inhibition of pancreatic α-amylase from pigs with non-significant differences (glucosides of pelargonidin > malvidin > cyanidin > delphinidin > peonidin); petunidin glucoside was not studied. Interestingly, anthocyanins acylated with hydroxycinnamic acids, originating from black carrots, inhibited pancreatic α-amylase even more than nonacylated ones (Kaeswurm et al., 2020). Purple maize extract containing both acylated and nonacylated anthocyanins inhibited pancreatic α-amylase *in vitro* (Zhang et al., 2019). In the case of pigmented potatoes, the literature is not unanimous. Moser et al. (2018) reported that the phenolic extracts from purple and red potatoes did not inhibit pancreatic α-amylase from pigs *in vitro*, whereas Kalita et al. (2018) showed that the phenolic extracts from purple, red, yellow, and white potatoes inhibited pancreatic α-amylase, but the extracts of purple and red potatoes were more efficient. The effect of the phenolic metabolites on pancreatic α-amylase is, however, modest compared to cyanidin glucoside and sambubioside (protocatechuic acid > phloroglucinaldehyde > caffeic acid > 4-hydroxybenzaldehyde > ferulic acid > vanillic acid > *p*-coumaric acid > homovanillic acid > 4-hydroxybenzoic acid > hippuric acid) (Ho et al., 2017).

Continuing on to the intestinal α-glucosidase, the brush-border enzyme of the small intestine with sucrase and maltase activities, a structure-dependent inhibition has been discovered. Of 18 isolated, nonacylated anthocyanins, pelargonidin glucoside inhibited α-glucosidase the most *in vitro*. The inhibitory activity of anthocyanidins followed the order of pelargonidin > malvidin > peonidin > delphinidin > petunidin > cyanidin, and for glycosides, rutinosides > glucosides and arabinoside > glucoside > galactoside (Xu et al., 2018). Cyanidin and its glycosides were inactive maltase inhibitors also in other studies (Akkarachiyasit et al., 2010; Iwai et al., 2006), whereas cyanidin-3-rutinoside slightly inhibited rat intestinal maltase (Adisakwattana et al., 2011) and cyanidin-3-sambubioside actively (yeast α-glucosidase and porcine pancreas maltase) (Iwai et al., 2006). Intestinal sucrase of rats was inhibited only modestly by cyanidin and its glycosides (cyanidin-3-galactoside > cyanidin-3-glucoside > cyanidin), whereas cyanidin-3,5-diglucoside did not inhibit sucrase at all (Akkarachiyasit et al., 2010). Other studies reported that cyanidin and cyanidin-3-glucoside did not inhibit sucrase (Iwai et al., 2006), whereas cyanidin-3-rutinoside (Adisakwattana et al., 2011) and cyanidin-3-sambubioside (Iwai et al., 2006) did.

Acylation, again, increases the inhibitory activity of the anthocyanin on α-glucosidase. Two diacylated purple sweet potato anthocyanins, cyanidin- and peonidin-3-*O*-[2-*O*-(6-*O*-feruloyl-glucose)-6-*O*-caffeoyl-glucose]-5-*O*-glucose), were shown to strongly inhibit the maltase activity of rat intestinal α-glucosidase, but not the sucrase activity. Acylation to caffeic and ferulic acids was essential as deacylation drastically decreased the inhibitory activity (Matsui et al., 2001). Furthermore, rats fed with sucrose, glucose, or maltose and a diacylated anthocyanin from purple sweet potato (peonidin-3-*O*-[2-*O*-(6-*O*-feruloyl-glucose)-6-*O*-caffeoyl-glucose]-5-*O*-glucose) showed suppressed glycemia and reduced serum insulin only in the case of maltose, implying that the hypoglycemic effect of the diacylated anthocyanin was related to inhibiting the maltase activity (Matsui et al., 2002). The anthocyanin

fraction of black carrot (Esatbeyoglu et al., 2016) and purple sweet potato (Esatbeyoglu et al., 2017) inhibited α-glucosidase dose-dependently *in vitro*. The phenolic extract of purple potatoes inhibited α-glucosidase more than those of the red, yellow, and white cultivars (Kalita et al., 2018). However, two purple potato cultivars and one white potato cultivar, but not the red cultivars, had a modest inhibitory effect on rat intestinal α-glucosidase *in vitro* (Moser et al., 2018). Phenolic metabolites (protocatechuic acid, gallic acid, vanillic acid, protocatechuic aldehyde, ferulic acid, 4-hydroxybenzaldehyde, syringic acid, and chlorogenic acid) did not inhibit yeast α-glucosidase statistically significantly (Barik et al., 2020) but inhibited intestinal α-glucosidase (protocatechuic acid > phloroglucinaldehyde > caffeic acid > ferulic acid > 4-hydroxybenzaldehyde > vanillic acid > *p*-coumaric acid > homovanillic acid > 4-hydroxybenzoic acid > hippuric acid) (Ho et al., 2017).

8.2 | Inhibition of absorption of glucose

After the dietary carbohydrates are decomposed to monosaccharides by the digestive enzymes, glucose is transported to the enterocytes of the small intestine, and from there, to the systemic circulation. In Caco-2 cell monolayers *in vitro*, cyanidin was the most effective in inhibiting the uptake of glucose followed by delphinidin > malvidin > cyanidin-3-glucoside > delphinidin-3-glucoside (Barik et al., 2020). Also, a grape anthocyanin extract rich in malvidin-3-glucoside decreased the uptake of glucose in Caco-2 (Faria et al., 2009). *Ex vivo*, the uptake was decreased by cyanidin-3-rutinoside in rat jejunums (Hassimotto et al., 2008) and by delphinidin and delphinidin-rich maqui berry extract in mouse jejunal mucosa (Hidalgo et al., 2014, 2017). Considering acylated anthocyanins, both the semipurified extracts of purple potatoes and purple carrots decreased the intestinal glucose uptake (Zhang et al., 2017), and the phenolic extracts of purple, red, and white potatoes decreased the uptake across the Caco-2 cell monolayer *in vitro* (Moser et al., 2018). However, the anthocyanin fraction of purple carrots did not affect the glucose uptake to Caco-2/TC-7 cells *in vitro* (Esatbeyoglu et al., 2016). Moreover, phenolic metabolites of anthocyanins inhibited the absorption of glucose across the Caco-2 cell monolayer (4-hydroxybenzaldehyde > gallic acid > ferulic acid > syringic acid > chlorogenic acid); 4-hydroxybenzaldehyde, gallic acid, and ferulic acid were more efficient than the investigated nonacylated anthocyanins (Barik et al., 2020).

The suggested molecular mechanisms for the reduced absorption of glucose are not unambiguous. As anthocyanins and glucose may be taken up by the same transporters, competitive inhibition via steric hindrance has been suggested (Adisakwattana et al., 2011; Castro-Acosta, Lenihan-Geels, et al., 2016; Faria et al., 2009; Hidalgo et al., 2014; Zhang et al., 2017). Downregulation of the gene transcription of the glucose and fructose transporters (SGLT1, GLUT2, and GLUT5) may be another mechanism; however, Barik et al. reported that the selected, but unnamed, anthocyanidins and nonacylated anthocyanins did not have an effect. On the contrary, the phenolic metabolites were shown to downregulate the transcription of the genes of SGLT1 (chlorogenic acid > gallic acid > syringic acid > 4-hydroxybenzaldehyde > vanillic acid), GLUT2 (chlorogenic acid > gallic acid > 4-hydroxybenzaldehyde > vanillic acid > ferulic acid > protocatechuic acid), and GLUT5 (protocatechuic aldehyde > ferulic acid) (Barik et al., 2020). Delphinidin inhibited the intestinal glucose absorption by activating the free fatty acid receptor 1 (FFA1/GPR40), but anthocyanin glycosides did not (Hidalgo et al., 2017; Kato et al., 2015).

8.3 | Increased uptake of glucose into muscle and adipose tissues

Delphinidin-3-sambubioside-5-glucoside increased the uptake of glucose in rat L6 muscle cells (Rojo et al., 2012). Cyanidin, cyanidin-3-glucoside, cyanidin-3-sambubioside, and phenolic metabolites (caffeic acid, *p*-coumaric acid, ferulic acid, phloroglucinaldehyde, 4-hydroxybenzaldehyde, and vanillic acid) enhanced the uptake of glucose into human myotubes *in vitro* (Ho et al., 2017), possibly via enhancing the expression of GLUT4. GLUT4 is an insulin-dependent glucose transporter in the muscle and adipose tissues, and increased expression and translocation of GLUT4 to the cell surfaces leads to increased uptake of glucose in the tissues from circulation (Uldry & Thorens, 2004). Cyanidin-3-rutinoside increased GLUT4 expression and glucose uptake in human adipocyte cell model *in vitro* (Choi et al., 2017), and cyanidin-3-glucoside and its phenolic metabolite, protocatechuic acid, increased the uptake of glucose into human omental and murine adipocytes with and without stimulating the cells with insulin by enhancing the expression and translocation of the GLUT4 glucose transporters (Scazzocchio et al., 2011). Furthermore, the increased expression of GLUT4 due to the effect of chronic intake of cyanidin-3-glucoside was detected in the adipose tissues collected from sacrificed diabetic mice (Sasaki et al., 2007). In insulin-resistant adipose tissue cell model (3T3-L1) with decreased ability to intake glucose, purple maize extract rich in acylated and nonacylated

anthocyanins restored the glucose uptake *in vitro* (Zhang et al., 2019).

The enhanced uptake of glucose into muscle and adipose tissues may occur via phosphorylation (activation) of adenosine monophosphate (AMP) activated protein kinase (AMPK) as studied with nonacylated anthocyanins. AMPK cascade regulates the catabolic and anabolic energy metabolism reaction pathways (Hardie & Hawley, 2001) and its activation leads to, for example, enhanced uptake of glucose via increased translocation of GLUT4 to the cell membrane (Kurth-Kraczek et al., 1999). Nonacylated cyanidin-3-glucoside activated AMPK leading to enhanced expression of GLUT4 and the uptake of glucose in muscle model cells (rat L6 myotubes) *in vitro* (Kurimoto et al., 2013). After chronic consumption of blueberry anthocyanins by diabetic rats, AMPK was activated and expression of GLUT4 was increased in skeletal muscle and white adipose tissue of the sacrificed rodents (Takikawa et al., 2010).

Increased uptake of glucose to adipocytes by GLUT4 may occur also by activating the insulin signaling pathway, the PI3K/Akt (phosphoinositide 3 kinase/protein kinase B) pathway. Cyanidin-3-rutinoside increased the uptake of glucose into adipocyte model cells (3T3-L1) via PI3K/Akt pathway by phosphorylating (activating) IRS-1 (insulin receptor substrate 1) and Akt, and increasing the expression of PI3K. Cyanidin-3-rutinoside did not activate AMPK (Choi et al., 2017). Protocatechuic acid, the well-recognized phenolic metabolite of anthocyanins, may increase the uptake of glucose and translocation of GLUT4 by interacting in an undefined way with the insulin receptor and affecting the insulin signaling pathway as it activates IRS-1 and Akt in human visceral adipocytes *in vitro*. When IRS-1, Akt, and PI3K were specifically inhibited, uptake of glucose and translocation of GLUT4 did not occur. Protocatechuic acid also activated AMPK (Scazzocchio et al., 2015). In mice fed with purple sweet potato extract and HFD for 20 weeks, the hepatic insulin signaling pathway (IRS-1/Pi3K/Akt) was enhanced as compared with the group fed with the HFD alone showing impaired pathway (Zhang et al., 2013).

8.4 | Production of adipocytokines

In adipose tissue, the expression of GLUT4 may also be enhanced via adipocytokines. Adipocytes, in addition to being an energy storage, secrete biologically active adipocytokines. Adiponectins, for example, activate the insulin signaling pathway via PI-3K and AMPK of skeletal muscle and hepatocytes, increase the uptake of glucose in muscle cells, and suppress gluconeogenesis in the liver (Yamauchi et al., 2002). Interestingly, cyanidin, but not cyanidin-3-glucoside, enhanced the secretion of leptin and adiponectin in adipocytes collected from rats and treated *ex vivo*; AMPK activation was suggested as the molecular mechanism (Tsuda et al., 2004). Purple sweet potato extract rich in acylated anthocyanins decreased the amount of leptin in 3T3-L1 adipocytes *in vitro* (Ju et al., 2011). *In vivo*, the gene expression of adiponectin was upregulated after a 12-week administration of a purple corn extract rich in cyanidin-3-glucoside also containing acylated cyanidin-3-(6′′-malonyl-glucoside) and peonidin-3-(6′′-malonyl-glucoside) (Huang et al., 2015).

in vitro, nonacylated cyanidin-3-glucoside and protocatechuic acid increased adiponectin levels in human omental adipocytes and 3T3-L1 adipocytes via upregulating the gene transcription of PPARγ (peroxisome proliferator-activated receptor gamma), leading to increased translocation of GLUT4 to the membranes (Scazzocchio et al., 2011). The PPARγ is a member of the nuclear receptor superfamily regulating lipid and glucose homeostasis, expression of GLUT4 and expression of adipose tissue molecules, such as adiponectin, resistin, leptin, and TNF-α (TNF-α) among other roles (Ahmadian et al., 2013; Iwaki et al., 2003). The inflammatory adipocytokines monocyte chemoattractant protein-1 and TNF-α, which are present in obese and diabetic states and downregulate GLUT4, were decreased after the chronic intake of nonacylated cyanidin-3-glucoside in diabetic mice. It was also suggested that this may further decrease the expression of another adipocytokine, RBP-4 (retinol-binding protein 4) (Sasaki et al., 2007). RBP-4 interferes with insulin signaling in muscle tissue and contributes to insulin resistance in obese and diabetic states (Yang et al., 2005). In another study, blueberry anthocyanins downregulated RBP4 in diabetic rats (Takikawa et al., 2010).

8.5 | Inhibition of gluconeogenesis

Although only traces of intact acylated anthocyanins are likely to reach the liver, effects of anthocyanins on hepatic cells have been studied. A 7-week daily administration of mainly acylated anthocyanins of purple sweet potatoes alongside with HFD inhibited the gene expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase of diabetic mice in comparison to HFD without anthocyanins (Jiang et al., 2020). A daily 8-week intake of purple potato extract rich in acylated anthocyanins to diabetic mice resulted in decreased hepatic messenger RNA level of the *G6PC* gene encoding glucose-6-phosphatase and *TBC1D1* encoding TBC1D1 responsible for the translocation of the insulin-dependent GLUT4 to cellular surface (Chen et al., 2020). *in vitro*, glucose production was decreased in the hepatic cell

model, HepG2, by cyanidin-caffeoyl-*p*-hydroxybenzoyl-sophoroside-5-glucoside and peonidin-3-caffeoyl-sophoroside-5-glucoside, but not with peonidin-3-(6′′-caffeoyl-6′′′-feruloyl-sophoroside)-5-glucoside, all extracted from purple sweet potatoes (Jang et al., 2019). Cyanidin-malonyl-glucoside extracted from red lettuce did not inhibit the hepatic glucose production in the H4IIE rat hepatoma cells *in vitro*, but the red lettuce extract rich in phenolic compounds and aforementioned acylated anthocyanin did (Cheng et al., 2014). The nonacylated anthocyanins (delphinidin-3-sambubioside-5-glucoside and maqui berry anthocyanins) inhibited the hepatic glucose production in a type II diabetes rat cell model (H4IIE) *in vitro*. Furthermore, the maqui berry anthocyanins downregulated glucose-6-phosphatase in the presence of insulin (Rojo et al., 2012). The inhibition of the gluconeogenic enzymes may occur via activating hepatic AMPK as detected in long-term studies with diabetic mice fed with black soybean seed coat extract rich in nonacylated anthocyanins (Kurimoto et al., 2013), blueberry extract (Takikawa et al., 2010), and purple corn extract containing phenolic acids, nonacylated and acylated anthocyanins (cyanidin-3-(6′′-malonyl-glucoside), and peonidin-3-(6′′-malonyl-glucoside)) (Huang et al., 2015). Furthermore, the long-term fasting glycemia may be improved via the Akt-mediated activation of FoxO1, as an 8-week daily oral administration of cyanidin-3-glucoside to diabetic mice resulted in its inhibition, leading to decreased glucose-6-phosphatase and phosphoenolpyruvate carboxykinase and decreased fasting state blood glucose (Guo et al., 2012).

8.6 | Increased incretin secretion

GLP-1 (glucagon-like peptide-1) and GIP-1 (gastric inhibitory peptide) are incretin hormones stimulating the secretion of insulin glucose-dependently. Regarding nonacylated anthocyanins, a meal of black currant juice increased the postprandial GLP-1 and GIP in healthy volunteers (Castro-Acosta, Smith, et al., 2016). *in vitro*, delphinidin-3-rutinoside, delphinidin, and malvidin enhanced the secretion of GLP-1 in the murine enteroendocrine GLUTag L cells, whereas the other studied aglycones, glucosides, or rutinosides did not. The suggested mechanism was by increased release of cytosolic Ca^{2+} and activation of CAMKII (calmodulin-dependent kinase II), possibly via a G-protein coupled receptor GPR40/120 (Kato et al., 2015). However, the black carrot fraction rich in acylated anthocyanins did not affect GLP-1 secretion in the GLUTag cells *in vitro* (Esatbeyoglu et al., 2016).

8.7 | Radical scavenging capacity

In the postprandial state, berry-meals rich in nonacylated anthocyanins increase postprandial plasma antioxidant capacity in healthy volunteers (Cao & Prior, 1998; Edirisinghe et al., 2011; Kay & Holub, 2002; Matsumoto et al., 2002; Mazza et al., 2002; Mertens-Talcott et al., 2008; Prior et al., 2007; Seymour et al., 2014), and the serum anthocyanin content positively correlates with the postprandial antioxidant status (Mazza et al., 2002). However, contradictory results exist (Garcia-Alonso et al., 2009; Jin et al., 2011; Mathison et al., 2014). Considering acylated anthocyanins, a meal of purple potatoes did not increase the plasma antioxidant capacity of healthy volunteers (Moser et al., 2018; Ramdath et al., 2014). A meal of purple potatoes raised the plasma antioxidant capacity in a mixed study population of normal weight ($n = 5$), overweight ($n = 2$), and obese ($n = 1$) volunteers first at 30 min and then at 2 h, and further increased it toward the last sampling point, from 4 to 8 h (Vinson et al., 2012). Three *in vitro* studies in which purple potatoes, purple sweet potatoes, and red cabbage rich in acylated anthocyanins were incubated in a gastrointestinal model suggest that the antioxidant capacity is due to the intact gastric acylated anthocyanins and their subsequent phenolic degradation products (Kubow et al., 2016, 2017; Podsędek et al., 2014). Chronic supplementation of purple sweet potato extract and HFD to mice for 20 weeks resulted in decreased amount of hepatic reactive oxygen species (Zhang et al., 2013).

Regardless of their low concentration, the antioxidant capacity of acylated anthocyanins in cells has been studied *in vitro*. Purple potato and purple carrot polyphenolic extracts showed strong cellular antioxidant activity in Caco-2 cells, but the effect was not dose dependent (Zhang et al., 2016). In another study, the polyphenolic extract from purple tomatoes was administered to an *in vitro* gastrointestinal digestion model, and both the cell-based antioxidant activity analysis with MCF-10A cells and the chemical-based antioxidant activity assays revealed that the gastric and intestinal conditions lead to significant degradation of the antioxidant activity, but the activity was still well retained so that the phenolic compounds may act as antioxidants within the cells after absorption (Li et al., 2014).

Anthocyanins may protect from oxidative stress as they have a planar, delocalized, π-conjugated ring system, which enables their strong antioxidant properties via scavenging different free radicals, such as DPPH (2,2-diphenyl-1-picrylhydrazyl), ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), and OH radicals, by donating hydrogens and electrons, and via the

resonance effect of the aromatic nucleus. Considering the structure–antioxidant activity relationships, the importance of *o*-dihydroxystructure of cyanidin and trihydroxylation of delphinidin, the increased number of hydroxygroups in the B-ring, and a free 3-OH in the C-ring are required for the most efficient radical scavenging activity. Mono- and dimethoxygroups decrease the activity, as do glycosylation (Ali et al., 2016; Kähkönen & Heinonen, 2003; Rice-Evans et al., 1996; Wang et al., 1997). Interestingly, cyanidin-3-coumaroyl-xyloside-glucoside)-5-galactoside showed similar activity as the monoglucosides (Kähkönen & Heinonen, 2003).

Acylated anthocyanins are radical scavengers as detected *in vitro* with diacylated anthocyanins from purple sweet potatoes (Jang et al., 2019; Luo et al., 2018) and monoacylated nasunin from eggplants (Noda et al., 1998). Interestingly, acyl group enhances the radical scavenging activity of anthocyanins, diacylated more than monoacylated (Azuma et al., 2008; Matsufuji et al., 2007; Wiczkowski et al., 2013). An *in vitro* study conducted with purified cyanidin-derived anthocyanins of red cabbage showed that the antioxidant activity of the acylated anthocyanins followed the descending order of the acyl groups of sinapic acid > caffeic acid > *p*-coumaric acid (Wiczkowski et al., 2013), and with the diacylated anthocyanins of purple sweet potato, the order was caffeic acid > ferulic acid > *p*-hydroxybenzoic acid (Luo et al., 2018). Petanin, found also from eggplants, showed DPPH radical scavenging activity in the order of delphinidin-3-rutinoside-caffeoyl-5-glucoside > delphinidin-3-rutinoside-coumaroyl-5-glucoside > petunidin-3-rutinoside-coumaroyl-5-glucoside (petanin) > delphinidin-3-glucoside > delphinidin-3-rutinoside (Azuma et al., 2008). At pH 7.4, both mono- and diacylation with hydroxycinnamic acids increased the radical scavenging capacity (ORAC) in cyanidin glycosides (Stintzing et al., 2002) and monoacylation with *p*-coumaric acid increased the antioxidative activity of malvidin glycosides measured by linoleic acid oxidation (Tamura & Yamagami, 1994).

As regards purple potatoes, their double-triple increase in antioxidant activity as compared to white potatoes (Brown et al., 2003) is related to their anthocyanin concentration (Andre et al., 2007; Lachman et al., 2009). Pigmented potatoes show antioxidant activity even as snack products (Nemś et al., 2015; Nemś & Pęksa, 2018). An anthocyanin-rich extract prepared from cooked purple potatoes showed a slightly decreased but still strong antioxidant activity when compared to the noncooked sample as measured with a DPPH test after administrating to an *in vitro* gastrointestinal model (Ombra et al., 2015). However, comparing the results between different studies and different anthocyanin structures, including aromatic acylation, is challenging, due to dissimilar methods, solvent systems, pH, concentrations of anthocyanins, and purity of the anthocyanins, and drawing conclusions on the basis of *in vitro* models may be misleading.

8.8 | Endogenous antioxidant defense

Consumption of anthocyanin-rich foods may increase the endogenous antioxidative defense; however, this has received little attention in the research. Chronic administration of foods rich in acylated anthocyanins to rodents increased the activity of glutathione peroxidase (GPx) and catalase (CAT) (red cabbage extract, diabetic rats) (Buko et al., 2018), GPx, reduced glutathione (GSH) and superoxide dismutase (SOD) (purple sweet potato extract + HFD, mice) (Zhang et al., 2013), SOD and GPx (purple potato flakes, rats) (Han et al., 2006), SOD and GPx (purple sweet potato anthocyanin extract, diabetic mice) (Jiang et al., 2020), and SOD, CAT, GPx, GSH (purple potato extract, diabetic rats) (Strugała et al., 2019). *in vitro*, pure nonacylated anthocyanins and anthocyanidins upregulated GR, GPx, and GST in rat hepatocyte Clone 9 cells; cyanidin, cyanidin-3-glucoside, delphinidin, and malvidin showed the best efficiencies (Shih et al., 2007). The purple potato and purple carrot extracts increased the activities of antioxidant enzymes (CAT, GPx, and SOD) and glutathione reductase in Caco-2 cells *in vitro* (Zhang et al., 2016). Additionally, purple carrots rich in acylated anthocyanins decreased cyclo-oxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS) (Olejnik et al., 2016), and purple sweet potato extract lowered COX-2 *in vitro* (Ju et al., 2011).

The clinical trials suggest a late response possibly due to phenolic metabolites. An acute consumption of cranberry juice rich in nonacylated anthocyanins increased GSH and SOD 24 h after the meal in healthy volunteers (Mathison et al., 2014). Another study showed no effect on plasma glutathione within 8 h after an acute intake of bilberry extract rich in nonacylated anthocyanins in healthy volunteers, but transcription of NAD(P)H dehydrogenase (NQO1) increased and transcription of heme oxygenase 1 (HO-1) decreased. The transcription of Nrf2, the regulator of NQO1 and HO-1, was also increased (Kropat et al., 2013). Nrf2 is an anti-inflammatory, redox-sensitive transcription factor, which binds to the antioxidant response element (ARE) promoter area inducing, for example, transcription of antioxidative enzymes (GPx, glutathione reductase GR) and detoxifying enzymes (glutathione-S-transferase GST) (Ma, 2013). The bioactive compound was possibly phloroglucinaldehyde, a phenolic metabolite, as the anthocyanins and other studied metabolites did not induce ARE promoter activity *in vitro* (Kropat et al., 2013). *in vitro*, transcription of Nrf2 may be enhanced by cyanidin-3-glucoside

in TNF-α exposed Caco-2 cells (Ferrari et al., 2016). Acylated anthocyanins may not affect Nrf2 and HO-1 as such as investigated *in vitro* with an anthocyanin-rich fraction of purple sweet potatoes and Huh-7 cells; however, the polyphenolic fraction did. The target genes of Nrf2, *Gpx4*, and *GSS* encoding glutathione peroxidase 4 and glutathione synthetase, respectively, were not affected when the fractions were added to hepatic HepG2 cells (Esatbeyoglu et al., 2017).

Lastly, the NF-κB and MAPK pathways may be altered by anthocyanins. NF-κB is a nuclear factor responsible for the transcription of a number of genes, including those encoding cytokines, chemokines, immunoreceptors, cell adhesion molecules, acute phase proteins, growth factors, and enzymes, such as SOD, and pro-inflammatory enzymes COX-2 and iNOS (Barnes, 1997; Pahl, 1999). *in vitro*, the purified nonacylated anthocyanins of bilberries and black currants (Karlsen et al., 2007) and cyanidin-3-glucoside (Ferrari et al., 2016) suppressed NF-κB in TNF-α exposed Caco-2 cells and LPS-induced monocytes, respectively. A 20-week feeding of mice with HFD supplemented with purple sweet potato extract inhibited the activation of hepatic IκB kinase (IKKβ)/NF-κB and JNK1 and improved the IRS-1/Pi3k/Akt insulin signaling pathway when compared to the HFD alone (Zhang et al., 2013). JNK1 is part of the MAPK family (mitogen-activated protein kinases), which are inflammation and cytokine-stimulated kinases regulating, for example, cell differentiation, mitosis, and apoptosis (Johnson & Lapadat, 2002). *in vitro*, anthocyanin-rich extracts of purple potatoes and purple carrots suppressed lipopolysaccharide-induced phosphorylation of JNK and IkBα, indicating both MAPK and NF-κB pathways, in mucosal innate immune cells. Purple potato anthocyanins were more efficient and restored the expressions to the level of normal control cells (Zhang et al., 2017).

9 | FUTURE PROSPECTS

To fully unravel the potential of acylated anthocyanins as a part of foods and diets and as food colorants and bioactive compounds in functional foods, careful consideration of the following issues is critical in future research.

The model food compositions The current lack of standardized methods and requirements for the analytical characterization of the model foods leads to a challenge to compare and differentiate the bioactive components and to understand the chemical composition. Careful chemical characterization of the study meals especially for phenolic compounds and nutrients is a necessity, and the purity of studied extracts and anthocyanin fractions should be evaluated.

Matrix effects and bioactive doses Anthocyanins are rarely ingested as such, and thus comparing the effect of the purified acylated anthocyanins, extracts and the original anthocyanin-rich foods provide insight on the possible matrix effects and the antagonist and synergistic effects of other flavonoids and dietary compounds. To provide specific guidance for food industry and consumers, structure–activity relationships and the optimal bioactive doses of acylated anthocyanins are yet to be determined.

Structural characteristics Understanding the effect of different acyl groups and acylation sites on health effects, gut microbiota and metabolic fate in the gastrointestinal tract requires more comparative studies with pure anthocyanins and foods rich in structurally different anthocyanins.

Methodologies The research on acylated anthocyanins has been mainly focused on mechanistical *in vitro* studies and animal studies which do not completely represent the complex postprandial metabolism of humans, and small-scale clinical trials. Clinical trials with greater number of study subjects are still needed to confirm the current observations, and long-term studies with whole foods rich in acylated anthocyanins and normal diets should be conducted. Comparing the health effects of isolated acylated and nonacylated anthocyanins, and extracts and deacylated extracts in the same clinical trial would increase the understanding of their *in vivo* effects. Application of untargeted omics approach may provide a comprehensive view on the impact of acylated anthocyanins on gene expression, gut microbiota, and metabolomics profiles, leading to an enhanced understanding of the physiological effects of these compounds.

Broadening endpoints to metabolites As the circulating concentration of anthocyanins in blood is low, the future studies should investigate the role of anthocyanin degradants and phenolic metabolites in the health effects of anthocyanins instead of focusing on the bioavailability of the parent compounds as such. Use of labeled acylated anthocyanins would benefit the future clinical trials to link the metabolites, parent anthocyanins, and clinical outcomes. There is still a gap in understanding the *in vivo* degradation of acylated anthocyanins. *in vitro* studies show that acylated anthocyanins may be more stable in the upper gastrointestinal tract than nonacylated ones and thus more acylated anthocyanins may reach the gut microbiota, which possibly affects the breakdown time frames and quantities of the formed phenolic metabolites.

Development of food applications Lastly, more investigation is needed to harness the potential of acylated anthocyanins in food development applications as a natural colorant and a part of functional foods. For example, replacing the current colorants from food products, stability tests,

and multisensory hedonic liking tests should be evaluated in different food products.

10 | CONCLUSION

Acylation affects the chemistry, bioavailability, absorption, and metabolism of anthocyanins. The molecule is more active as a radical scavenger, with altered polarity and larger by its size, preventing nucleophilic attack of water, and thus acylated anthocyanins provide natural, stable colorants for industrial purposes. Acylation may stabilize anthocyanins in the upper gastrointestinal tract, and act there as antioxidants. The gastric absorption mechanism differs from that of nonacylated anthocyanins. Some of the acylated anthocyanins reaching the intestine are absorbed by intestine epithelial cells via glucose transporters, and gut microbiota may hydrolyze acylated anthocyanins. The degradants formed in the small and large intestine show further radical scavenging activity. The acylated anthocyanins reaching small intestine may inhibit enzymes related to carbohydrate digestion. The bioavailability of anthocyanins as such is extremely low and acylation decreases it even further, and thus investigating their degradation to phenolic metabolites presents an interesting research target for the future. The potential of acylated anthocyanins as bioactive compounds altering carbohydrate metabolism and decreasing postprandial inflammation is promising even though the current studies vary in methods, target outcomes, anthocyanin vehicles, structures and purities of anthocyanins, as well as dosage and administration timeframes. This work encourages incorporating foods rich in acylated anthocyanins to everyday diets and further research and food development on acylated anthocyanins.

AUTHOR CONTRIBUTIONS

Johanna Jokioja: Conceptualization; Funding acquisition; Writing-original draft; Writing-review & editing. Baoru Yang: Conceptualization; Funding acquisition; Project administration; Supervision; Writing-review & editing. Kaisa M. Linderborg: Conceptualization; Funding acquisition; Project administration; Supervision; Writing-original draft; Writing-review & editing

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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