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# Some Anthocyanins Could Be Efficiently Absorbed across the Gastrointestinal Mucosa: Extensive Presystemic Metabolism Reduces Apparent Bioavailability

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**ABSTRACT:** Despite the accumulating evidence supporting the health effects of anthocyanins, their plasma concentrations were found to be very low. However, 30 and 56% of cyanidin 3-glucoside (Cy-3-glc) and pelargonidin 3-glucoside (Pg-3-glc) were found as protocatechuic acid (PCA) and 4-hydroxybenzoic acid, respectively, in plasma following oral administration in humans. Second, 12.4% of $^{13}C$ was recovered from urine and breath following oral ingestion of [$^{13}C$]-Cy-3-glc in humans. The actual percentage of [$^{13}C$]-Cy-3-glc absorbed across the gastrointestinal wall could be higher because of the involvement of enterohepatic recycling in the disposition of anthocyanins. In animal studies, high total urinary recoveries were found following oral ingestion of $^{14}C$-labeled anthocyanins. Third, anthocyanins seem to be efficiently absorbed following in situ gastric and intestinal perfusions in rats. Therefore, some anthocyanins could be efficiently absorbed from the gastrointestinal lumen, undergo extensive first-pass metabolism, and enter the systemic circulation as metabolites.

**KEYWORDS:** *anthocyanin, absorption, bioavailability, first-pass metabolism, cyanidin 3-glucoside, pelargonidin 3-glucoside*

Anthocyanins constitute the largest group of water-soluble pigments in plants, being responsible for the blue, purple, and red colors of many fruits, flowers, and leaves. Many comprehensive reviews have been published on the health benefits of anthocyanins.[1−5] Recently, with the availability of food composition databases for individual flavonoids,[6,7] many population-based investigations have been conducted on the correlation between the intake of individual flavonoids and health conditions in the general population. It was found that intake of foods rich in anthocyanins is associated with a reduced risk of diseases such as cardiovascular disease,[8−11] diabetes mellitus,[12] and cancer.[13,14] Food intervention studies have shown that administration of fruits rich in anthocyanins can improve clinical and biomedical indices in patients with various health conditions.[15−18]

Bioavailability of anthocyanins was the subject of several excellent reviews.[19−24] In contrast to the accumulating evidence supporting their health effects, the plasma concentrations of anthocyanins were found to be low. The percentage of intact anthocyanins excreted in urine was found to be <0.1% in human studies. In animal studies, absolute bioavailabilities of anthocyanins were found to be only 0.26−1.8% when intravenous administrations were used for comparisons.[25−30] This led to a common perception that the absorption of anthocyanins is inefficient.

The possibility of first-pass metabolism for anthocyanins was briefly mentioned in several papers without providing literature evidence.[19,21,31] This paper summarizes, for the first time, the existing body of evidence indicating that the observed low apparent bioavailabilities of some anthocyanins could be due to their extensive presystemic metabolism, rather than poor absorption from the gastrointestinal lumen.

## HIGH PLASMA METABOLITE CONCENTRATIONS FOLLOWING ADMINISTRATION OF ANTHOCYANINS

In humans, 30−44% of the consumed cyanidin 3-glucoside (Cy-3-glc) was found as protocatechuic acid (PCA) in plasma following administration of blood orange juice[32] and black raspberries[33] (Figure 1). The maximum concentration of PCA was found to be about 0.5 $\mu$M following administration of blood orange juice containing 71 mg of Cy-3-glc in humans.[32] Only 0.02% of the administered Cy-3-glc (maximum concentration = 1.9 nM) was found in the bloodstream in its original form. Similarly, plasma 4-hydroxybenzoic acid (maximum concentration = 2.5 $\mu$M), a metabolite of pelargonidin 3-glucoside (Pg-3-glc), accounted for 54−56% of strawberry Pg-3-glc ingested in volunteers.[34]

The high plasma concentrations of the phenolic acid metabolites are in contrast to the low concentrations of their corresponding anthocyanins. There is currently no consensus on whether the phenolic acids were produced within the gastrointestinal lumen before being absorbed or after absorption into the intestinal wall. First-pass metabolism or presystemic metabolism refers to the metabolism of drugs or food components in the intestine wall or liver during the absorption process. During absorption, drugs or food components are carried via the mesenteric vessels to the portal vein and then to the liver before entering the systemic circulation.[35] The following is evidence from the literature in favor of the notion that most plasma 4-hydroxybenzoic acid and

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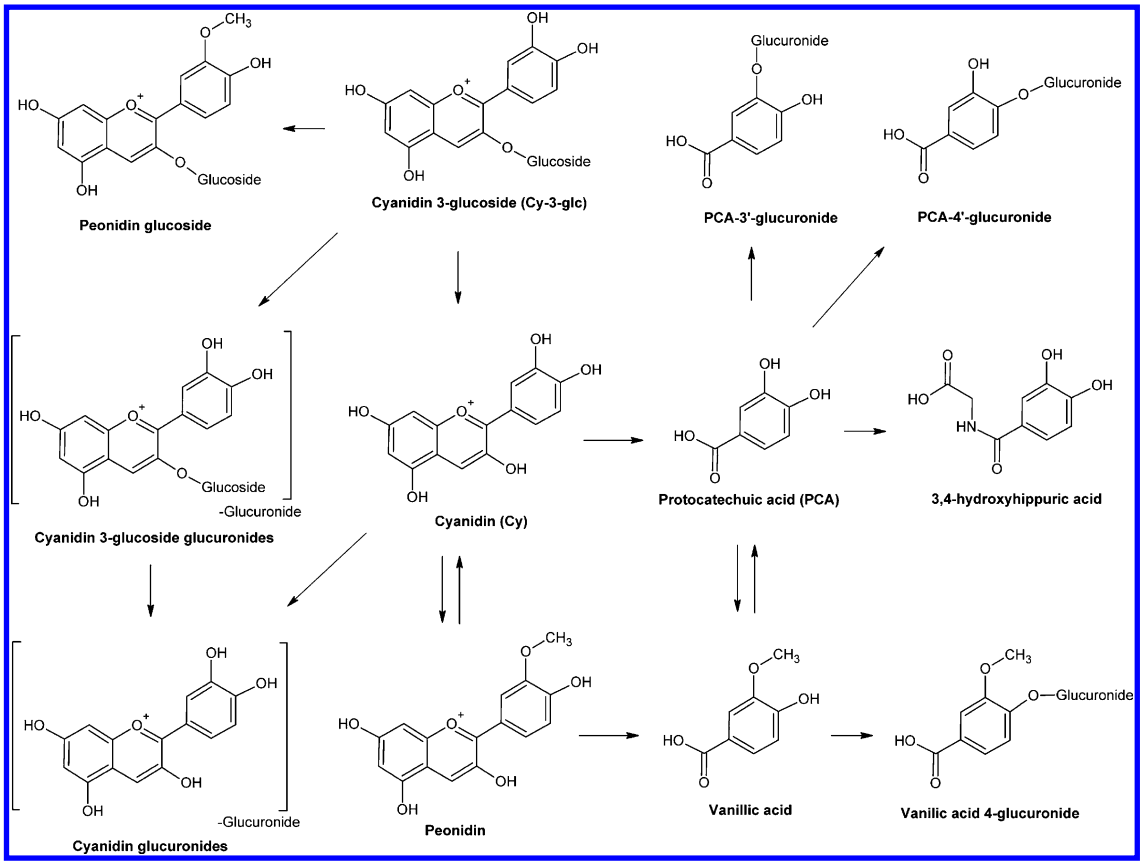


**Figure 1.** Major metabolic pathways of cyanidin 3-glucoside.[29,34,46,62,78,84,91]

PCA are formed during first-pass metabolism in the intestinal wall or liver (Figure 2).

**Anthocyanins Could Efficiently Permeate into the Intestinal Wall.** Native anthocyanins found in the small intestine tissue amounted to 7.5% of the ingested dose 2 h following administration of black raspberries in rats.[36] In another study, rats were administered a blackberry anthocyanin-enriched diet for 15 days. The jejunum contained 605 nmol/g tissue of Cy-3-glc and its methylated and glucurono-conjugated metabolites.[37] The exceptionally high anthocyanin concentrations in gastrointestinal tissues were in great contrast to their concentrations in blood. In addition, cell culture studies also demonstrated that anthocyanins can permeate Caco-2 cell monolayers.[38−40] This suggests that anthocyanins undergo extensive first-pass metabolism and enter the systemic circulation as metabolites. The concentrations in gastrointestinal tissues are similar to those used in some in vitro studies on the health effects of anthocyanins.[1−5] Anthocyanins could achieve pharmacologically relevant local concentrations and exert their protective effects in the gastrointestinal wall.[41−43]

**Cy-3-glc Is Not a Substrate of $\beta$-Glucosidase or Lactase-Phlorizin Hydrolase.** Unlike a number of other flavonoids, Cy-3-glc was found not to be a substrate of cytosolic $\beta$-glucosidase[44] or lactase-phlorizin hydrolase.[31] Because lactase-phlorizin hydrolase was localized to the apical membrane of small intestinal epithelial cells, it was suggested that some flavonoids are deglycosylated on the luminal surface before being absorbed.[31] Whereas this could be true for the substrates of the luminally exposed lactase-phlorizin hydrolase such as quercetin-3-glucoside,[31] it is unlikely to be the case for Cy-3-glc. This is consistent with the fact that intact Cy-3-glc can accumulate in the intestine tissue in rats following oral administration.[36,37] This is also consistent with the observation that only the glycosides, not their metabolites, were recovered in the intestinal lumen following perfusion of anthocyanins.[45] Thus, Cy-3-glc can probably be absorbed intact into the gastrointestinal wall, undergo extensive first-pass metabolism, and enter the systemic circulation as metabolites.

The mechanism of cleavage of the sugar moiety of Cy-3-glc remains to be established. With regard to the further breakdown of the anthocyanin aglycones, it was found that human liver microsomes can metabolize Cy to PCA, which is further metabolized to form three glucuronide conjugates.[46] Similarly, pelargonidin is metabolized to 4-hydroxybenzoic acid, which is further metabolized to form two additional glucuronide conjugates by human liver microsomes.

**Chemical Decomposition in the Gastrointestinal Tract Is Unlikely To Account for Most Plasma Phenolic Acid Metabolites for the Relatively Stable Anthocyanins.** Because phenolic acids such as PCA can be absorbed from the gastrointestinal tract,[33,47,48] it was suggested that the phenolic acids could be produced by chemical decomposition within the intestinal lumen before being absorbed. However, the literature outlined below indicates that chemical degradation is unlikely to be the main source of plasma 4-hydroxybenzoic acid and PCA following oral administration of Pg-3-glc and Cy-3-glc, respectively.

Many anthocyanins are rather stable in the upper gastrointestinal tract. Anthocyanins are known to be stable in the acidic environment of the stomach.[49−51] As absorption of anthocyanins was shown to take place in the stomach,[49,52−54]


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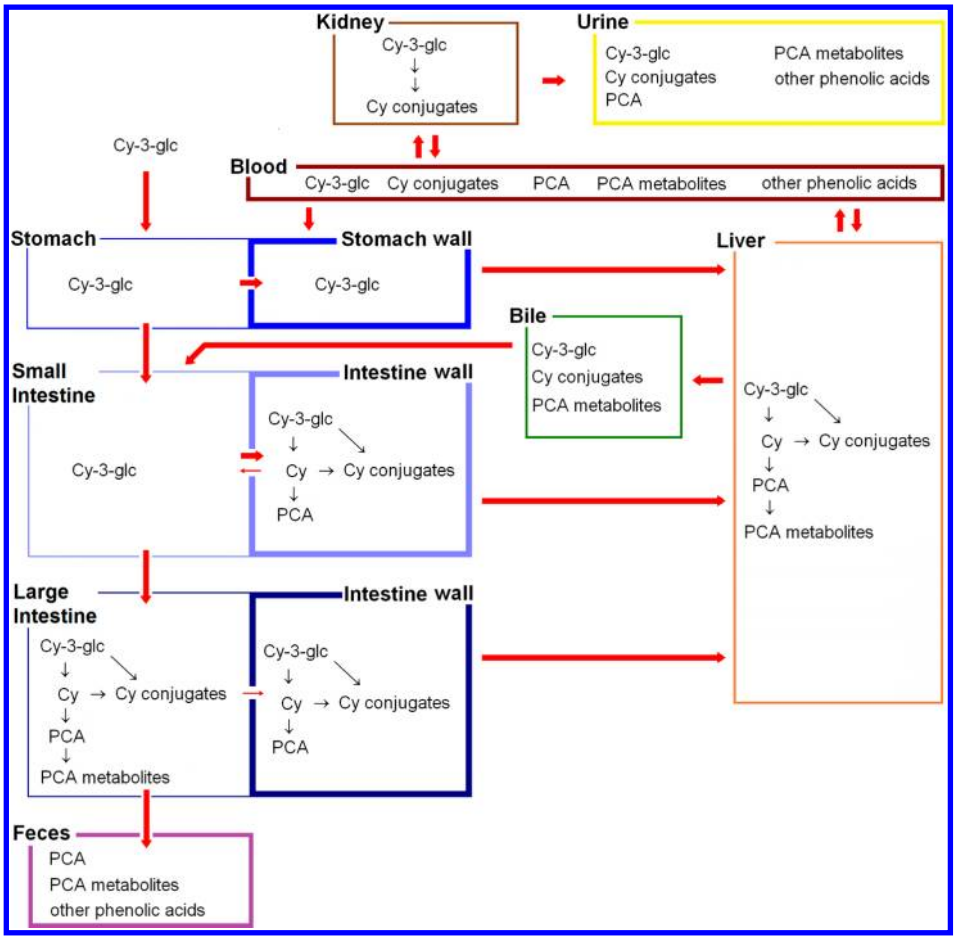


**Figure 2.** Schematic diagram of the absorption, first-pass metabolism, and further disposition of Cy-3-glc following its ingestion.[37,92−94] Abbreviations: Cy, cyanidin; Cy-3-glc, cyanidin 3-glucoside; PCA, protocatechuic acid.

significant amounts of anthocyanins could be absorbed in the stomach in their native forms.

In the small intestine, many anthocyanins such as Pg-3-glc are stable in this relatively neutral environment.[46] In an in vitro study, strawberry anthocyanin (mostly Pg-3-glc) decomposition was minimal when incubated at 37 °C in a simulated intestinal fluid (pH7) for 48 h.[55] Thus, it is unlikely that chemical decomposition of Pg-3-glc was primarily responsible for the high blood concentrations of 4-hydroxybenzoic acid in the absence of microbiota.

For those anthocyanins that do decompose, there seems to be a delay between the loss of anthocyanin aglycones and the formation of the phenolic acids probably due to the relatively stable transition products.[46,56,57] This delay could further reduce the concentrations of phenolic acids in the upper gastrointestinal tract. More detailed kinetic studies are needed to clarify the relationship between the disappearance of anthocyanins and the formation of their phenolic acid decomposition products.

In studies using ileostomists, the percentages of some anthocyanins remaining in ileal fluids did not seem to correlate with their stabilities.[58] For example, Cy-3-glc is far more stable than delphinidin 3-glucoside in simulated intestinal buffer,[50,59] but less of it remains in the ileal fluid following oral ingestion of wild blueberries.[58] These differences could be explained by the possibility that Cy-3-glc is more efficiently absorbed in the upper gastrointestinal system. A similar conclusion can also be derived from another study on Concord grape juice in ileostomists.[50] Cyanidin glycosides were found to be far more stable than delphinidin glycosides following in vitro incubation with simulated gastric and pancreatic juices, yet the percentages recovered in ileal fluid were comparable for the two anthocyanins following ingestion of 350 mL of the grape juice.

For the few anthocyanins that are unstable in the upper gastrointestinal tract, such as delphinidin 3-glucoside,[59] chemical degradation may play a role in the formation of their phenolic acid metabolites. A total of 40.7% of delphinidin 3-glucoside was found to remain in ileal fluid in ileostomists administered blueberries.[58] Therefore, 59.3% delphinidin 3-glucoside was either absorbed or decomposed before reaching the large intestine. On the other hand, delphinidin 3-glucoside was found to be absorbed into the bloodstream in its native form.[50,60,61] It is therefore perceivable that first-pass metabolism also contributes to the formation of the phenolic acid metabolites of delphinidin 3-glucoside.

**Gut Microbiota Decomposition Products May Not Be Extensively Absorbed.** In the large intestine, the microbiota can facilitate the formation of phenolic acid metabolites from anthocyanins.[50,55,62−70] However, they would not affect the plasma concentration versus time curve until a later time when anthocyanins reach the large intestine. The maximum rate of excretion of food components in ileal fluid took place at around 2 h when 1 L of apple juice or 300 g of blueberries was consumed by a group of ileostomists.[58] Most polyphenols passed the small intestine 4−8 h after the consumption of fruits or fruit juices.[50,58,71,72] The intestinal transition time would be

longer if solid food were ingested together with the fruits or fruit juices. Following administration of blood orange juice, plasma PCA concentrations increased rapidly and reached maximum concentrations at 2 h.[32] This is partly because anthocyanins can be absorbed from the stomach.[52,53] Thus, high plasma PCA concentrations were achieved before Cy-3-glc reached the large intestine and underwent microbiota decomposition.

Furthermore, only 5.9−28.3% of administered Cy-3-glc was excreted in ileal fluid from ileostomists administered blueberries, grapes, or raspberries.[50,58,71] Animal studies also indicated that Cy-3-glc is mostly absorbed in the stomach and upper part of the small intestine.[36,41,73,74] It is worth noting that fecal recoveries were 32.1 and 44.5% of administered [$^{13}$C]- or [$^{14}$C]-Cy-3-glc in humans[75] and mice,[76] respectively. This indicates that most Cy-3-glc entering the large intestine is excreted in feces. Thus, degradation products of Cy-3-glc may not be extensively absorbed from the large intestine.

Gut microbiota can produce large amounts of phenolic acids from those anthocyanins that reach the large intestine in large quantities.[50,58,71,72] In one study, the percentages remaining in ileal fluid relative to food content are in the following order: malvidin 3-arabinoside (85.1%) > petunidin 3-arabinoside (73%) > petunidin 3-galactoside (59.1%) > malvidin 3-galactoside (54.4%) > petunidin 3-glucoside (47.5%) > delphinidin 3-galacotoside (45.3%) > cyanidin 3-arabinoside (44.6%) > malvidin 3-glucoside (42.8%) > delphinidin 3-glucoside (40.7%) > delphinidin 3-arabinoside (37.8%) > cyanidin 3-galactoside (36.8%) > peonidin 3-glucoside (29.9%) > Cy-3-glc (28.3%).[58] It is perceivable that anthocyanins such as malvidin 3-arabinoside and petunidin 3-arabinoside would mostly be degraded by gut microbiota[65,66,77] and produce large quantities of metabolites.[68,69] However, the microbiota decomposition products may not be absorbed extensively into the bloodstream as is the case for Cy-3-glc. Further studies are needed to confirm the poor absorption of phenolic acids in the large intestine by introducing anthocyanins or their phenolic acid metabolites directly into the large intestine.

To summarize the above discussion, first-pass metabolism probably plays an important role in the formation of 4-hydroxybenzoic acid and PCA from Pg-3-glc and Cy-3-glc, respectively, after they are absorbed from the upper gastrointestinal lumen.

In addition to the phenolic acid metabolites, the bioavailabilities of some anthocyanins were found to be higher when phase II metabolites were also accounted for. The major metabolites of anthocyanins recovered in urine were glucuronidated and/or methylated conjugates.[78−83] Enzymes responsible for these biotransformations may include UDP-glucuronosyl transferase, UDP-glc dehydrogenase, or catechol-*O*-methyltransferase (COMT) located in the small intestine, liver, or kidney. For example, the bioavailability of delphinidin 3-rutinoside was found to be 2.67% when its 4′-methylation product was also accounted for in both the urine and bile of rats.[28] In other studies, total urinary excretion of anthocyanins and their metabolites was found to be 0.26−1.8% of the anthocyanins ingested.[29,30]

## STUDIES USING $^{13}$C- OR $^{14}$C-LABELED ANTHOCYANINS

In a recent human study using [$^{13}$C]-Cy-3-glc, 12.4% of the $^{13}$C-label was recovered from urine and breath following oral ingestion.[75] The actual percentage of [$^{13}$C]-Cy-3-glc absorbed across the gastrointestinal wall should be higher because of involvement of bile secretion in the disposition of anthocyanins (Figure 2). In mice administered [$^{14}$C]-Cy-3-glc, a high concentration of radioactivity was found in bile, indicating an important role of bile secretion in the disposition of Cy-3-glc.[76] Extensive bile secretion of [$^{14}$C]-PCA was also found following intraperitoneal injection in rats,[84] probably as its conjugates.[46] Extensive bile secretion of delphinidin 3-rutinoside and its 4′-methylated metabolite was also observed in rats.[28]

In human studies, an indication of extensive involvement of enterohepatic recycling is a second peak observed on the plasma concentration versus time curve. The second peak is due to the secretion of anthocyanins accumulated in bile into the duodenum and their subsequent reabsorption. This phenomenon was observed for delphinidin-3-glucoside and petunidin-3-glucoside in healthy volunteers administered Concord grape juice.[50] A second peak was also visible for malvidin-3-glucoside and mean plasma total anthocyanin concentration following consumption of red wine[85] and purple carrot juice,[86] respectively, in human volunteers. A similar pattern of the plasma concentration versus time curve has been observed for phase II metabolites of PCA.[75] In another study, a second peak of PCA was visible following administration of strawberries (containing Cy-3-glc as a minor component) in human volunteers.[34] This could also be due to enterohepatic recycling where conjugates of PCA were secreted into the duodenum and underwent cleavage to release the free PCA either within the intestinal lumen or during first-pass metabolism. Thus, due to the extensive involvement of enterohepatic recycling, the percentage of [$^{13}$C]-Cy-3-glc absorbed across the gastrointestinal wall would be higher than the 12.4% found in urine and breath in humans.[75]

Animal studies were also conducted on the absorption of [$^{14}$C]-Cy-3-glc. In a study in mice, the pharmacokinetics of anthocyanins were investigated using Cy-3-glc labeled with $^{14}$C on its B-ring.[76] At 3 h after oral administration of [$^{14}$C]-Cy-3-glc, 3.3% of the radioactivity was detected in urine, mostly as metabolites. Plasma PCA concentrations were not measured in this particular study. However, on the basis of the HPLC chromatograms in the paper, it is evident that the concentrations of metabolites in plasma are many times higher than that of Cy-3-glc.[76] In a human study, there was a 42-fold higher abundance of $^{13}$C-labeled metabolites relative to [$^{13}$C]-Cy-3-glc.[75]

In the above-mentioned study in mice, it is projected that the total percentage of radioactivity excreted in urine would be about 4.4% of the administered [$^{14}$C]-Cy-3-glc under the assumption that urine excretion of Cy-3-glc and its metabolites is proportional to plasma concentrations.[76] This total urinary recovery of Cy-3-glc is similar to that found in humans administered [$^{13}$C]-Cy-3-glc (5.4%).[75] This percentage represents the lower limit of Cy-3-glc absorbed into the systemic circulation including the metabolites produced during its presystemic metabolism. In addition to urine excretion, the absorbed [$^{14}$C]-Cy-3-glc and its metabolic products can also be eliminated from the body by secretion through bile. Bile contained a high concentration of radioactivity (7.81 Bq/mg tissue in bile as compared to 0.35 Bq/mg tissue in liver),[76] indicating a prominent role for bile in the disposition of [$^{14}$C]-Cy-3-glc. Indeed, 13% of PCA was found to be excreted in bile (as its conjugates) following intraperitoneal injection in rats.[84] In addition to bile, expiration of volatile metabolites or

autoxidation products into the air was found to be another elimination pathway for [$^{13}$C]-Cy-3-glc in humans, accounting for 6.9% of the administered dose.[75] Taken together, it is probable that the actual percentage of [$^{14}$C]-Cy-3-glc absorbed across the gastrointestinal wall is much higher than the observed total urine recovery (4.4%).

In another study using $^{14}$C-labeled flavonoids, between 16 and 43% of radioactivity was found to be excreted in urine 24 h after oral administration of the anthocyanin glycoside fractions biosynthesized by grape cell suspension cultures.[87] These results are also consistent with the high percentage absorbed suggested by the above-mentioned studies.[32−34,49,59,75]

## IN SITU GASTRIC AND INTESTINAL ABSORPTION OF ANTHOCYANINS

Efficient absorption of anthocyanins was also observed following in situ gastric and intestinal perfusion in rats. High plasma anthocyanin concentrations were found in both portal vein and systemic circulation following gastric perfusion.[52,53] In another study, the observed decreases of bilberry anthocyanins in the gastric fluid were 19−37% following 30 min in situ gastric absorption.[49] With regard to Cy-3-glc, the percentage absorbed was found to be 23% within the stomach under the experimental conditions. In a cell culture study, anthocyanins were found to be able to cross MKN-28 cell monolayers (differentiated adenocarcinoma stomach cells), probably via a saturable transporter mechanism.[54] Anthocyanins are stable under acidic conditions and do not degrade in simulated gastric juice.[49−51] In humans, anthocyanins were found in the bloodstream within minutes of consumption.[88] Five-fold higher urine concentrations of anthocyanins were observed in two patients following administration of a bilberry extract (Mirtoselect) via nasal intubation into the stomach rather than the jejunum.[89] It is therefore likely that anthocyanins can be absorbed from the stomach in their native forms.

An in situ perfusion model was used to evaluate the absorption of anthocyanins in the jejunum and ileum of rats. Between 10.7 and 22.4% of the anthocyanins were absorbed following perfusion at a flow rate of 0.75 mL/min.[59] The percentage of Cy-3-glc absorbed was found to be 22.4%. Degradations of anthocyanins in simulated intestinal buffer (pH 6.6, incubated at 37 °C for 45 min) are in the following order: Cy-3-glc (percentage decomposed = 2.32%), malvidin 3-glucoside (3.63%), cyanidin 3-galactoside (4.13%), and cyanidin 3-rutinoside (5.15%).[59] Cy-3-glc was found to be more stable when present in blackberry extract with only 0.69% decomposed. Delphinidin glycosides were the least stable, with a percentage of degradation of 9.31%. Their decline in the perfusion solution was not reported as a result of absorption. Therefore, it is reasonable to assume that the decreases of most anthocyanins in the perfusion solutions were mainly due to absorption rather than chemical degradation.

## FUTURE PERSPECTIVES AND CONCLUSION

In addition to the research needed to confirm or clarify some issues outlined above, it is now clear that many studies conducted on anthocyanins need to be repeated in light of the formation of their phenolic acid metabolites, the plasma concentrations of which are 1−2 magnitudes higher than their respective parent compounds.[32−34] These studies include bioavailability studies of individual anthocyanins; studies using ileatomist volunteers; studies on the effects of food matrices on the absorption of anthocyanins; animal studies on the tissue concentrations of anthocyanins; and ex vivo absorption studies using human or animal tissues and cell culture models. It is also apparent that different anthocyanins are vastly different in their stability, absorption, metabolism, and elimination.[24] These differences are important in determining the sites of their health effects and the contribution of microbiota and chemical degradation to their disposition. Thus, different anthocyanins should be studied individually to ease the interpretation of experimental results. Cy-3-glc and Pg-3-glc are two anthocyanins extensively studied because they are predominant components in fruits such as blackberries[90] and strawberries.[15] Other purified or synthesized anthocyanins could also be used for studies using animal models and human volunteers.[75]

In conclusion, the extensive literature indicates that absorption and first-pass metabolism play important roles in the disposition of some anthocyanins, such as Cy-3-glc and Pg-3-glc, in the upper gastrointestinal tract. Metabolites such as PCA and 4-hydroxybenzoic acid could be responsible for the systemic health effects of anthocyanins. High permeations of native anthocyanins into the gastrointestinal wall also suggest that anthocyanins could achieve pharmacologically relevant local concentrations and exert their protective effects in the gastrointestinal system.

## AUTHOR INFORMATION

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## ABBREVIATIONS USED

Cy, cyanidin; Cy-3-glc, cyanidin 3-glucoside; Pg-3-glc, pelargonidin 3-glucoside; PCA, protocatechuic acid

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