Anthocyanins and Curcumin: Possible Abilities of Prevention of Diabetes and Obesity via Stimulation of Glucagon-Like Peptide-1 Secretion and Induction of Beige Adipocyte Formation

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Summary There is growing interest in the health benefits of natural plant pigments such as anthocyanins and curcumin. In this review, we introduce how these pigments can contribute to the prevention of diabetes and obesity by stimulating glucagon-like peptide-1 (GLP-1) secretion or inducing beige adipocyte formation. Of the anthocyanins, delphinidin 3-rutinoside (D3R) was shown to increase GLP-1 secretion. Pre-administered D3R-rich blackcurrant extract (BCE) significantly ameliorated glucose tolerance after intraperitoneal glucose injection in rats by stimulating the secretion of GLP-1 and subsequently inducing insulin secretion. D3R did not break down significantly in the gastrointestinal tract for at least 45–60 min after BCE administration. An increase in endogenous GLP-1 secretion induced by food-derived factors may help to reduce the dosages of diabetic medicines and prevent diabetes. Curcumin has various biological functions, including anti-obesity and anti-diabetic properties. However, high doses of curcumin have been administered in most animal and human trials to date, due mainly to the poor solubility of native curcumin in water and its low oral bioavailability. We demonstrated that a highly dispersible and bioavailable curcumin formulation (HC), but not native curcumin, induces the formation of beige adipocytes. Furthermore, co-administration of HC and artepillin C (a characteristic constituent of Brazilian propolis) at lower doses significantly induces beige adipocyte formation in mice, but administration of the same dose of HC or artepillin C alone does not. Our studies demonstrate that curcumin formulations or the co-administration of curcumin with other food-derived factors provide effects that native curcumin alone does not.

Key Words anthocyanins, curcumin, glucagon-like peptide-1, beige adipocyte, uncoupling protein 1

There is growing interest in the health benefits of natural plant pigments such as anthocyanins and curcumin. Anthocyanins are a group of naturally occurring phenolic compounds responsible for the color of many flowers, fruits (particularly berries), and vegetables. Anthocyanins have a variety of health-related functions, including anti-obesity and anti-diabetes activities (1). These favorable activities cannot be explained by their antioxidant properties alone; indeed, anthocyanin-derived metabolites are known to contribute to these functions (1).

Curcumin is a polyphenol found in turmeric and is used as a spice, food coloring, and herbal medicine. In addition to its antioxidant and anti-inflammatory activities, like anthocyanins, curcumin is reported to have various health benefits, such as anti-diabetes and anti-obesity activities (2).

In this review, we introduce how these pigments help prevent diabetes and obesity by stimulating glucagon-like peptide-1 (GLP-1) secretion or inducing beige adipocyte formation.

Delphinidin 3-rutinoside (D3R)-rich blackcurrant extract (BCE) improves glucose tolerance by increasing the release of GLP-1 secretion

GLP-1 is a gut hormone secreted from enteroendocrine L-cells, and is recognized as one of the incretins that stimulate glucose-dependent insulin secretion and β-cells proliferation (3, 4). Increasing endogenous GLP-1 secretion by food-derived factors may be an effective approach and decrease the doses of other diabetic medicines, and help prevent diabetes (5). We investigated dietary components with GLP-1 secretion-stimulating effects and identified several candidates, including anthocyanins (5, 6). Delphinidin 3-rutinoside (D3R) is abundant in blackcurrants and displays a strong GLP-1 secretion-stimulating effect in vitro (7). Several studies have reported that dietary blackcurrant extract (BCE) lowers blood glucose levels and ameliorates glucose tolerance in mice and rats (8, 9). In addition, BCE drinks decrease the postprandial blood glucose concentration in humans (10) but the mechanism remains unclear. We hypothesized that BCE improves hyperglycemia and glucose tolerance due to its stimulation of GLP-1 secretion. Our studies clearly demonstrated that pre-administration of D3R-rich BCE (1 mg D3R; i.e., 5 mg BCE/kg body weight) significantly reduced the concentration of plasma glucose and increased the levels of...
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plasma insulin after intraperitoneal glucose injection in rats (11). Moreover, the plasma concentrations of the total and active forms of GLP-1 were significantly elevated in the portal vein after the administration of BCE (11) (Fig. 1). D3R did not break down significantly in the gastrointestinal tract for at least 45–60 min after BCE administration, suggesting that BCE-induced GLP-1 secretion is mediated mainly by D3R and not by its degradation products (11).

Curcumin formulation or co-administration of curcumin formulation and another food factor effectively induces beige adipocyte formation

Mammals possess two types of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT), which have physiologically distinct functions. WAT stores excess energy as triglycerides, whereas BAT releases excess energy through heat production from mitochondria. Thermogenesis in BAT requires the action of thermogenic uncoupling protein 1 (UCP1), which causes mitochondrial proton leakage and the generation of heat instead of ATP. Brown-like adipocytes (also called “beige adipocytes”) are induced in WAT and release excess energy as heat through a process mediated by UCP1, as in BAT (12). Beige adipocyte induction is an important therapeutic target for treating obesity and various related disorders. The induction of beige adipocytes has been linked in many studies to various food-derived factors.

The results of several experimental animal and clinical trials indicate that curcumin helps suppress the accumulation of body fat (13, 14). However, high doses of curcumin were administered in most animal and human studies to date, mainly because native curcumin is poorly soluble in water and has low oral bioavailability (2).

Various curcumin formulations have been designed and developed to address this (2). Such formulations might be effective in harnessing the various biological activities of curcumin against diabetes, obesity, and other conditions. A highly water-dispersible and bioavailable curcumin formulation (HC) was previously developed using surface-controlled submicron particle formation technology (15). In addition, the co-administration of several food-derived factors enhanced their bioactivity compared with the administration of each factor alone. For example, green tea containing O-methylated catechin and ginger extract enhanced the anti-allergic effects of green tea (16), and a combination of vitamin A and epigallocatechin gallate strongly suppressed tumor growth (17). These combination effects may reduce the required functional doses of food-derived factors, providing bioactivity at a reasonable dose.

We demonstrated that HC (4.5 mg native curcumin, i.e., 15 mg HC/kg body weight, 4 wk) significantly induced the formation of beige adipocytes in inguinal WAT (iWAT) in mice (18). However, administration of the same dose of native curcumin did not have this effect. The formation of beige adipocytes in iWAT by HC is likely due to the production of local norepinephrine (NE) from the accumulated alternatively activated macrophages (18) (Fig. 2). Our findings showed that HC has significant bioactive effects in vivo at lower doses compared with native curcumin.

We also demonstrated that co-administration of low-dose HC (1.5 mg native curcumin/kg) and artepillin C (a characteristic constituent of Brazilian propolis, 5 mg/kg) for 4 wk significantly induced the development of beige adipocytes in mouse iWAT, but administration of the same dose of HC or artepillin C alone did not (20). Artepillin C enhances the generation of local NE from accumulated alternatively activated macrophages in iWAT mediated by HC (20) (Fig. 2). These findings may demonstrate that co-administration of food-derived factors is effective for enhancing their bioactivity and reducing their required doses.

Fig. 1. D3R-rich BCE significantly ameliorates glucose tolerance by stimulating GLP-1 secretion, followed by the induction of insulin secretion.

Fig. 2. HC significantly induces beige adipocyte formation. Induction is mediated by the production of local NE from accumulated alternatively activated macrophages in iWAT. Co-administration of HC and artepillin C at lower doses significantly induces beige adipocyte formation. ArtC enhances the generation of local NE from accumulated alternatively activated macrophages in iWAT mediated by HC. This figure was reprinted from (18 and 19) with permission.
Conclusion
Our studies clearly indicated that D3R-rich BCE may help prevent diabetes and reduce the required dosages of diabetes drugs. Exploring the link between long-term consumption of D3R or D3R-rich BCE and metabolite concentrations might help elucidate the health benefits of anthocyanins. Curcumin is a significant source of food-derived factors for preventing diabetes and obesity, and HC will help effectively exploit the various biological activities of curcumin. Although several points need to be considered in future studies on the health benefits of curcumin, as described in our previous reviews (2, 19), our studies demonstrate that curcumin formulations or the co-administration of curcumin with another food-derived factor (e.g., artepillin C) provide effects that native curcumin alone does not. Functional food research on anthocyanins and curcumin is expected to contribute greatly to studies on the overall health benefits of these compounds.

Disclosure of state of COI
No conflicts of interest to be declared.

REFERENCES