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Award Review

Physiological functions of poorly absorbed polyphenols via the glucagon-like peptide-1

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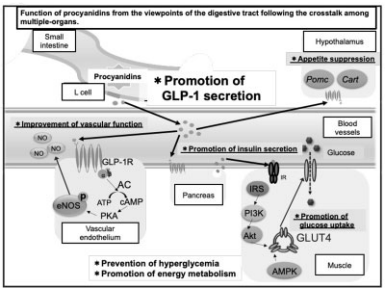
Abstract

Polyphenols are compounds of plant origin with several documented bioactivities related to health promotion. Some polyphenols are hard to be absorbed into the body due to their structural characteristics. This review focuses on the health beneficial effects of polyphenols mediated by intestinal hormones, particularly related to the systemic functions through the secretion of glucagon-like peptide-1 (GLP-1), an enteric hormone that stimulates postprandial insulin secretion. GLP-1 is secreted from L cells in the distal small intestine. Therefore, some poorly absorbed polyphenols are known to have the ability to act on the intestines and promote GLP-1 secretion. It has been reported that it not only reduces hyperglycemia but also prevents obesity by reduction of overeating and improves blood vessel function. This review discusses examples of health effects of polyphenols mediated by GLP-1 secretion.

Keywords: polyphenols, glucagon-like peptide-1, hyperglycemia, obesity, vascular function

Graphical abstract



The mechanisms of procyanidin of physiological functions.

Abbreviations: AMPK: AMP-activated protein kinase; BE: black soybean seed coat extract; C/EBPα: CAAT/enhancer binding protein α; cAMP: cyclic adenosine monophosphate; CLPr: cacao liquor procyanidin-rich extract; CVD: cardiovascular diseases; DP: degrees of polymerization; EGCG: epigallocatechin-3-gallate; ELISA: enzyme-linked immuno sorbent assay; eNOS: endothelial nitric oxide synthase; GI: gastrointestinal; GLP-1: glucagon-like peptide-1; GLUT4: glucose transporter 4; GSPE: grape seed–derived proanthocyanidins; ICR: Institute of Cancer Research; IR: insulin receptor; IRS: insulin receptor substrate; NO: nitric oxide; PKA: protein kinase A; PLC: phospholipase C; PPARγ: peroxisome proliferator-activated receptor γ; TRPM5: transient receptor potential cation channel, subfamily M, member 5; UCP: uncoupling proteins

Polyphenols are secondary metabolites found in vegetables, fruits, grains, bark, tea, and wine. These compounds exhibit several health benefits such as immune modulators, vasodilators, antioxidants, and preventing life-style diseases. Based on their diverse chemical structures, polyphenols are classified into phenolic acids, flavonoids, stilbenes, and lignans (Pandey and Rizvi 2009). Phenolic acids are a group of compounds with a phenolic ring and carboxylic acid. Most dietary polyphenols exist naturally in the form of esters, glycosides, or polymers, many of which are poorly absorbed by the intestine. In general, poorly absorbable polyphenols are defined as those that are absorbed into the body at only about 0.1%, and anthocyanins and condensed tannins belong to this category (Manach *et al.* 2004). One of the most extensively studied categories of polyphenols, are flavonoids. A majority of flavonoids are noncovalently bound to glucose in plants, and some are present as flavonoid oligomers such as epicatechin in cocoa. The hydrolysis of the glycoside form of flavonoids begins in the mouth where flavonoids are partially released from the food matrix by saliva (Walle *et al.* 2005). The low pH in the stomach facilitates the degradation of flavonoid oligomers into small units (Piskula 2000), but most flavonoids are hydrolyzed and further metabolized in the small intestine, where β-glucosidases cleave the

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glucose moiety from flavonoids and generate the aglycone form (Day *et al.* 1998; Walle *et al.* 2000). A large proportion of ingested flavonoids do not undergo hydrolysis or conjugation in the small intestine (Crespy *et al.* 1999) and are not absorbed (Landete 2012). Instead, these unabsorbed flavonoids reach the colon where they are metabolized by colonic bacteria into smaller molecules such as phenolic acids, which can be partially absorbed into the circulation. Specifically, some intestinal bacteria strains have the enzymatic activity of glucuronidase and glucosidase that can deconjugate the glucuronidated or glycosylated forms of flavonoids, and yield simple deconjugated products that are partially absorbed and metabolized by colonic enterocytes (Feng *et al.* 2018). It is thus assumed that polyphenols exert various functions during their passage through the gastrointestinal (GI) tract (Lan *et al.* 2023; Osakabe, Fushimi and Fujii 2022). In fact, it has been reported that polyphenols exert effects such as secretion of various hormones, regulation of enzyme activities, and nerve stimulation, starting in the intestines. Given the low bioavailability but relatively high concentrations of polyphenols in the GI tract following dietary ingestion, it is likely that the intestine might be a primary site for polyphenols to exert the observed metabolic actions (Barnes *et al.* 2011). This review introduces the effect of polyphenol on health beneficial functions via the promotion of incretin hormone secretion.

The gut is the largest endocrine organ in the body and releases an array of hormones, which play many key roles in physiological and metabolic regulation. Specifically, GI hormones secreted after a meal play a critical role in regulating appetite, food intake, and glucose homeostasis (Koliaki *et al.* 2020). Glucagon-like peptide-1 (GLP-1) is a well-studied incretin hormone secreted by L cells in the gut, the second largest population of enteroendocrine cells. Incretin hormones are defined as gut peptides that are secreted after ingesting nutrients and stimulate insulin secretion (Nauck and Meier 2018). The role of GLP-1 in maintaining glucose homeostasis is mediated through its receptor (GLP-1R). GLP-1 binding to its receptor triggers cyclic adenosine monophosphate (cAMP) signaling that augments glucose-stimulated insulin secretion from pancreatic β cells while inhibiting glucagon release from α cells. In addition, the activation of GLP-1 signaling promotes β-cell proliferation and survival, therefore preserving islet mass. Furthermore, GLP-1 slows the gastric emptying and gut mobility, and probably also targets its receptor in the hypothalamus to promote satiety, thereby reducing food intake. Moreover, it increases cardiac function as well as other physiological functions (Müller *et al.* 2019).

GLP-1 secretion is primarily stimulated by ingested nutrients. Glucose, fatty acid, and amino acid stimulation of GLP-1 secretion is largely mediated via their respective receptors. Schematic overview of nutrient-induced GLP-1 secretion from L cells is described in Figure 1. Emerging evidence shows that not only nutrients but also some polyphenols can induce GLP-1 secretion from L cells via various mechanisms. Specifically, polyphenols can function as ligands of G-protein–coupled receptors (GPCRs), or regulate intracellular signaling molecules to modulate GLP-1 secretion. Additionally, some polyphenols might indirectly cause GLP-1 secretion mediated by gut microbiota. In this way, polyphenols are also known to promote GLP-1 secretion and exert various physiological functions (Wang, Alkhalidy and Liu 2021).

Effects of polyphenols on secretion of GLP-1

GLP-1, insulin, and the peripheral actions of insulin are strongly influenced by dietary components. Macronutrients are the most notable examples, but polyphenols and other micronutrients have also been documented as important regulators. It is well established that the elevation of intracellular cAMP levels induces both transcription and secretion of GLP-1 via protein kinase A (PKA) and Epac, a camp-activated effector protein, so it is speculated that polyphenols that contribute to its regulation may be involved in promoting GLP-1 secretion. Several polyphenolic compounds have been found to regulate GLP-1 secretion via GPCRs or cAMP signaling pathway (Müller *et al.* 2019).

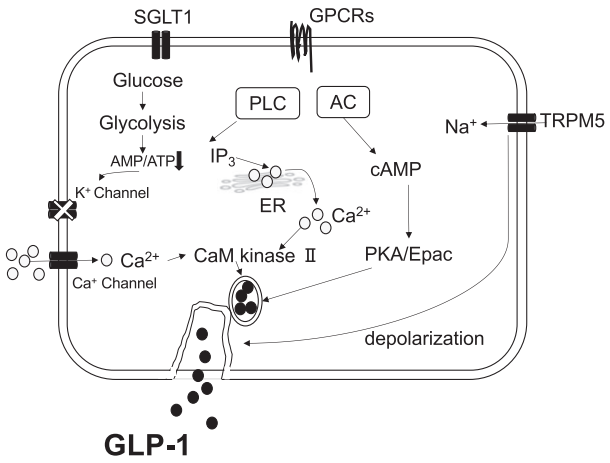

Figure 1. Schematic overview of nutrient-induced GLP-1 secretion from L cells. Abbreviations: AC: adenylyl cyclase; GLP-1: glucagon-like peptide-1; GPCRs: G-protein–coupled receptors; IP3: inositol trisphosphate; PLC: phospholipase C; PKA: protein kinase A; SGLT1: sodium/glucose cotransporter 1; TRPM5: transient receptor potential channel M5.

Specifically, GPCRs on the L cells might be activated by polyphenols to regulate GLP-1 secretion. Curcumin, a polyphenolic turmeric, has been found to induce GLP-1 secretion (Kato *et al.* 2017; Harada *et al.* 2022). It was reported that curcumin-induced GLP-1 secretion can be abrogated by the Ca^{2+} channel antagonist or IP3 receptor inhibitor, suggesting that both Ca^{2+} entry and release from intracellular store play a role in mediating curcumin-stimulated GLP-1 secretion, the latter of which may be due to the activation of phospholipase C (PLC). In addition, it has been already reported that GPR40/120 and 55 are involved in the induction of GLP-1 secretion of curcumin (Kato *et al.* 2017; Harada *et al.* 2022). Delphinidin 3-rutinoside, one of the anthocyanin derivatives from berry, increased GLP-1 secretion, via GPR40/120-mediated mechanism (Kato *et al.* 2015). As GPR40/120 are fatty acid receptors, it is unclear how above-discussed polyphenols are able to activate GPCRs.

The superfamily of bitter taste receptors (Tas2Rs) are expressed in the intestinal enteroendocrine cells (Wang, Alkhalidy and Liu 2021). Given that many dietary polyphenolic compounds are known to have a bitter taste, and they can interact with various taste receptors, in particular, Tas2Rsm, it is possible that Tas2Rs mediated polyphenols-induced GLP-1 secretion. While polyphenols have been found to activate several Tas2Rs, studies on whether polyphenols stimulate GLP-1 secretion via Tas2Rs are limited. Epigallocatechin-3-gallate (EGCG) is one of the most effective Tas2R39 activators among polyphenolic compounds. In addition, EGCG activated transient receptor potential ion channel A1 in the mouse clonal L-cell line (STC-1) (Kurogi *et al.* 2012), which was opened after Tsd2Rs activation to initiate the Ca^{2+} influx. EGCG has been reported to induce GLP-1 secretion in the mouse ileum segment (Song *et al.* 2015), and oral intake of EGCG stimulated GLP-1 secretion in mice and diabetic patients (Liu *et al.* 2014), suggesting that EGCG-stimulated GLP-1 might be mediated via Tas2R.

Recently, we also found that nonabsorbable polyphenols on procyanidin from cacao and black soybean seed coat induced GLP-1 secretion. Especially tetramer procyanidin on cinnamtannin A2 strongly increased GLP-1 secretion in the STC-1 cell line and in mice (Yamashita *et al.* 2013; Odongo *et al.* 2023). We extracted procyanidin oligomers from cacao liquor and acutely administered them individually to male Institute of Cancer Research (ICR) mice (10-μg/kg body weight, p.o.). The animals were sacrificed an hour after the treatment, and Enzyme-Linked Immuno Sorbent Assay (ELISA) analyses were used to quantify GLP-1 and insulin. Among the studied compounds (epicatechin, procyanidin B2, procyanidin C1, and cinnamtannin A2), cinnamtannin A2 increased GLP-1 and insulin concentration, and was the most bioactive overall. The same compound also exerts significant changes on skeletal muscle, by increasing insulin receptor (IR)-β and insulin receptor substrate (IRS)-1 phosphorylation. All compounds present in the cacao liquor samples are epicatechin and its oligomers, for example, procyanidin B1 is an epicatechin dimer, procyanidin C1 is an epicatechin trimer, and cinnamtannin A2 is an epicatechin tetramer. The evidence supports the hypothesis that the length of the procyanidin is key to the insulin-sensitizing results, as demonstrated by a lack of significant effects by the epicatechin monomer, dimer and trimer. In the STC-1 cell line, cinnamtannin A2 also induced GLP-1 secretion; however a low-degree of procyanidins, which are less than the tetramer, did not (Odongo *et al.* 2023). However, the mechanism of action of how cinnamtannin A2 promotes GLP-1 secretion is unknown, and more research is required. Grape seed–derived proanthocyanidins (GSPEs), which are composed of monomers or flavan-3-ols, dimers, trimers, tetramers, and oligomers of procyanidins, were found to increase GLP-1 secretion from clonal L cells as well as mouse ileum and colin segments (Casanova-Martí *et al.* 2017). This composition consists of compounds similar to the cacao polyphenols we used. The stimulatory action of GSPE on GLP-1 secretion might result from a rise in intracellular Na^+ influx via cation channel, transient receptor potential cation channel, subfamily M, member 5 (TRPM5), which leads to the depolarization and the opening of voltage-gated calcium channel, resulting in an increase in Ca^{2+} influx (González-Abuín *et al.* 2014), an essential step for exocytosis of GLP-1 granules. As condensed tannins are ligands of Tas2R, procyanidins might also activate taste receptors to regulate GLP-1 secretion. However, the degree of polymerization of procyanidins might affect their affinity for taste receptors (Soares *et al.* 2013); for example, procyanidin trimer C2 activates Tas2R5, but procyanidin dimer B2 fails to activate any Tas2Rs. Thus, studies on specific procyanidin should be performed to verify the activity of certain procyanidin on Tas2Rs.

Some polyphenols may promote GLP-1 secretion via activating cAMP-mediated intracellular signaling. Genistein, an isoflavone, hispidulin, a flavone, and coffee-derived polyphenols were shown to stimulate GLP-1 secretion mediated via increasing intracellular cAMP content. This review focuses on polyphenols that are difficult to absorb, so a detailed explanation will be omitted. These reports suggest that poorly absorbed polyphenols contribute to GLP-1 secretion from the GI tract, and that the mechanism of action may involve binding to GPCRs or taste receptors. Depending on the structure of each compound, the receptors it binds to differ.

Effect of procyanidins on antidiabetes and hyperglycemia through secretion of GLP-1

Since tetramer procyanidin induced GLP-1 secretion, we performed whether procyanidin prevent acute hyperglycemia. Procyanidin-rich compositions were extracted from cacao liquor and black soybean seed coat (BE) and prepared procyanidin fractions with different degrees of polymerization (DP), namely low-DP (DP $\leq$ 3) and high-DP (DP $\geq$ 4) fractions, from a cacao liquor procyanidin-rich extract (CLPr). These extracts and fractions were administered orally to ICR mice and their antihyperglycemic effects were examined. We found that CLPr and its fractions prevent postprandial hyperglycemia accompanied by an increase in the plasma GLP-1 level with or without glucose load. In the absence of glucose load, both fractions increased the plasma insulin level and activated its downstream signaling pathway in skeletal muscle, resulting in promotion of the translocation of glucose transporter 4 (GLUT4). Phosphorylation of AMP-activated protein kinase (AMPK) was also involved in the promotion of GLUT4 translocation. High- and low-DP fractions showed a similar activation of insulin and AMPK pathways. In conclusion, cacao liquor procyanidins prevent hyperglycemia by promoting GLUT4 translocation in skeletal muscle, and both the GLP-1-activated insulin pathway and the AMPK pathway are involved in the underlying molecular mechanism. In addition, among the procyanidin monomers to tetramers, cinnamtannin A2 showed the strongest effect in ICR mice (Yamashita *et al.* 2016). Preadministration of cinnamtannin A2 suppressed postprandial hyperglycemia in a dose-dependent manner. When mice received 0.1-10 μg/kg body weight of cinnamtannin A2, a significant effect was observed. Cinnamtannin A2 also showed a similar activation of insulin and AMPK pathways. Moreover, BE prevented hyperglycemia via GLP-1 secretion. The effect was stronger for procyanidin-rich fraction (PCBE) compared to BE (Odongo *et al.* 2023). Surprisingly, AMPK pathway as insulin-independent pathway was also activated by procyanidins. It was noteworthy that an antagonist for GLP-1 receptor exendin (9-39) canceled procyanidin-increased phosphorylation of AMPK (Hironao *et al.* 2020). These results suggest that procyanidin prevents hyperglycemia through GLP-1 secretion, and its underlying mechanisms contribute to both insulin and AMPK pathways. As described above, it is known that some polyphenol compounds prevent diabetes and hyperglycemia through the promotion of GLP-1 secretion.

Effect of procyanidins on antiobesity through secretion of GLP-1

GLP-1 is also known to contribute to obesity prevention by regulating energy metabolism and appetite. AMPK is a nutrient and energy sensor, enhances lipolysis, fatty acid oxidation, and ketogenesis, and attenuates lipogenesis and synthesis of cholesterol, fatty acids, and triglycerides (Long and Zierath 2006; Hardie, Ross and Hawley 2012. AMPK also enhances energy consumption through mitochondrial biogenesis and its related functions. Moreover, AMPK regulates adipocyte differentiation through modulation of the expression of peroxisome proliferator-activated receptor γ (PPARγ) and CAAT/enhancer binding protein α (C/EBPα) (Moseti, Regassa and Kim 2016). Thus, AMPK is a main target molecule for the prevention of obesity and hyperglycemia. Another important factor in regulation of obesity is uncoupling proteins (UCPs), which are key mitochondrial membrane transporters responsible for energy expenditure and thermogenesis. There are 2 types of adipocytes, white and brown adipocytes. White adipocytes store excess energy as fat, while brown ones play an important role in heat production because of having a large number of mitochondria expressing UCP1.

We have already reported the preventive effects of BE and CLPr on obesity and involvement of AMPK and UCPs using *in vivo* and

in vitro experiments (Kanamoto *et al.* 2011; Yamashita *et al.* 2012, 2020). Intake of BE for 2 weeks significantly increased phosphorylation of AMPK in the liver, skeletal muscle, and white adipose tissue (Yamashita *et al.* 2020). Long-term feeding of BE (Yamashita *et al.* 2020) and CLPr (Yamashita *et al.* 2012) prevented body weight gain and fat accumulation in white adipose tissue accompanied by upregulation of UCPs and downregulation of inflammatory cytokines in high-fat diet–fed C57BL/6 mice. Similar results were observed in KK-A^y mice fed a normal diet containing BE and C57BL/6 mice fed a high-fat diet containing CLPr. Procyanidins are also candidates for the active ingredients in BE because procyanidins from cacao and grape seed promoted AMPK phosphorylation in the liver, skeletal muscle, and adipose tissues *in vivo* and *in vitro*. As mentioned above, long-term feeding of BE increased UCPs in white and brown adipose tissue, suggesting that BE may increase energy expenditure through heat production. Recently, it has been reported that GLP-1R analog activates AMPK (Yang *et al.* 2020). We also found that the activation of AMPK by CLPr was canceled by pretreatment with a GLP-1R inhibitor (Hironao *et al.* 2020). Although the details are not clear, GLP-1 may be involved as one of the mechanisms of preventive effects on AMPK-mediated obesity.

GLP-1 is a major player in the gut-brain axis regulation of energy balance (Salehi and Purnell 2019). Many studies also suggest that GLP-1 receptor analogs promote weight loss mainly due to their inhibitory effect on food intake through the gut-brain axis (Valassi, Scacchi and Cavagnini 2008). GLP-1 binding to the GLP-1 receptors on the surface of neurons initiates intracellular signal transduction and activation of target genes, resulting in the synthesis and release of neuropeptides (pro-opiomelanocortin [POMC] and cocaine- and amphetamine-regulated transcript [CART]) with anorectic effects. GLP-1 can also be expected to contribute to the prevention of obesity by suppressing feeding. We also found that BE intake suppressed hyperphagia in KK-A^y mice and prevented obesity. Furthermore, at the end of the experiment, the concentration of GLP-1 in the plasma, as well as the expression levels of POMC and CART in the hypothalamus (preparing for paper submission), significantly increased in the BE-fed group. Thus, we also found that BE and CLPr, which are rich in procyanidins, prevent obesity through secretion of GLP-1. GLP-1 may play an important role in one of the mechanisms of the antiobesity effect of polyphenols.

Effect of procyanidins on improvement of vascular function via GLP-1 secretion

Vascular function is important to the pathogenesis of cardiovascular diseases (CVDs) (Sun *et al.* 2019). Vascular dysfunction caused by aging and vascular stiffness is associated with a risk of CVD. In addition, injurious stimuli such as oxidative stress, inflammation, diabetes, and obesity result in the dysfunction of vascular endothelial cells (Ding, Hashem and Triggle 2007; Tabit *et al.* 2010). Because vascular dysfunction is recoverable, it is important to detect vascular dysfunction as early as possible and improve it.

Nitric oxide (NO) regulates vascular functions by inducing vasodilation and inhibiting platelet aggregation in blood vessels (Michel and Vanhoutte 2010; Ghimire *et al.* 2017). A reduction in NO levels can trigger the onset of CVD. Therefore, increasing NO production in the vascular endothelium might prevent CVD and improve vascular function. NO is produced by endothelial nitric oxide synthase (eNOS). eNOS activation is regulated by several molecular mechanisms, including Ca^{2+}/calmodulin binding (Cai, Liu and Garcia 2008; Michel and Vanhoutte 2010), cAMP-dependent protein kinase, AMP-activated protein kinase5, and Akt (Fulton *et al.* 1999; Michel and Vanhoutte 2010). Of note, Akt promotes the phosphorylation of eNOS at Ser1177 residues in response to various stimuli, including insulin (Fulton *et al.* 1999). In addition, GLP-1 induced endothelium-dependent vasodilation (Golpon *et al.* 2001; Nathanson *et al.* 2009). It was reported that GLP-1 affected vascular endothelial cells and increased eNOS phosphorylation and subsequent NO production via the cAMP/PKA pathway *in vitro*. We found that BE increased NO production in the aortas of rats (Domae *et al.* 2019). Regarding the underlying mechanism of BE-induced NO production, BE promoted the phosphorylation of eNOS in vascular endothelial cells through GLP-1 secretion from intestinal cells. We confirmed that a GLP-1 receptor antagonist (exendin 9-39) inhibited BE-induced NO production and eNOS phosphorylation. To the best of our knowledge, this is the first report revealing that food components increase NO production in the aorta through GLP-1 secretion from intestinal cells. Recently, we also investigated the effect of black soybean consumption on the vascular function and oxidative stress associated with the polyphenol concentrations in healthy women (Yamashita *et al.* 2020, 2020). There was an observed improvement of the vascular stiffness, an increase in the plasma and urinary NO level, and a decrease in the oxidative stress. Black soybean has the potential to improve vascular function through increasing NO accompanied by GLP-1 secretion, although GLP-1 levels were not measured in this study. In addition, a previous study reported that mean blood pressure decreased significantly following oral administration of flavan-3-ols extracted from cocoa for 2 weeks in normal rats (Yu *et al.* 2021). In addition, it was reported that coffee polyphenol consumption improves postprandial hyperglycemia and vascular endothelial function, which is associated with increased GLP-1 secretion and decreased oxidative stress in healthy humans (Jokura *et al.* 2015). These results suggest that polyphenols that promote GLP-1 secretion contribute to improving vascular function and reducing oxidative stress.

Conclusion

Many polyphenols have low absorption efficiency due to their structure. However, recent research has revealed that it contributes to the action of the entire body, starting from the GI tract. Although this review only introduced the functionality of polyphenols mediated by the GI hormone GLP-1, there have been many reports targeting the intestine, such as functionality mediated by other hormones and intestinal microbiota. Although there is still hope that polyphenols may contribute to health, in the future it is necessary to develop research that takes into account signal transmission that occurs within the body, such as the network between multiple organs.

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Disclosure statement

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