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Regulatory Mechanism of Skeletal Muscle Glucose Transport by Phenolic Acids

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Abstract

Type 2 diabetes mellitus (T2DM) is one of the most severe public health problems in the world. In recent years, evidences show a commonness of utilization of alternative medicines such as phytomedicine for the treatment of T2DM. Phenolic acids are the most common compounds in non-flavonoid group of phenolic compounds and have been suggested to have a potential to lower the risk of T2DM. Skeletal muscle is the major organ that contributes to the pathophysiology of T2DM. Studies have shown that several phenolic acids (caffeic acid, chlorogenic acid, gallic acid, salicylic acid, *p*-coumaric acid, ferulic acid, sinapic acid) have antidiabetic effects, and these compounds have been implicated in the regulation of skeletal muscle glucose metabolism, especially glucose transport. Glucose transport is a major regulatory step for whole-body glucose disposal, and the glucose transport processes are regulated mainly through two different systems: insulin-dependent and insulin-independent mechanism. In this chapter, we reviewed recent experimental evidences linking phenolic acids to glucose metabolism focusing on insulin-dependent and insulin-independent glucose transport systems and the upstream signaling events in skeletal muscle.

Keywords: glucose metabolism, 5'AMP-activated protein kinase, insulin, glucose transporter, phytomedicine, phytochemical

1. Introduction

Diabetes is one of the most rapidly increasing chronic diseases in the world. According to the International Diabetes Federation [1], there are now 415 million adults aged 20–79 with diabetes worldwide, and there will be 642 million people living with the disease by 2040. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, which is due primarily to lifestyle factors and genetics. Numerous lifestyle factors, including excessive caloric intake, physical inactivity, cigarette smoking, and generous consumption of alcohol, are considered to be important to the development of T2DM [2]. T2DM care is usually managed by a multidisciplinary healthcare approach, which includes a combination of dietary restriction, exercise, hypoglycemic agents, and/or insulin. In present times, evidences show a commonness of utilization of alternative medicines for the treatment of T2DM.

A traditional herbal medicine, also called as phytomedicine, has been used since ancient time in many regions in the world. Phytomedicine is a medicine mainly derived from whole leaves, roots, stems, and plant extracts for promoting health and treating illness [3]. Plants produce numerous diversity of chemicals known as secondary metabolites through evolved secondary biochemical pathways. These secondary metabolites serve as defense compounds against herbivores or infection and thereby enhance their ability to survive. These compounds are also helpful for humans to protect themselves against diseases and are called phytochemical. Each type of fruit or vegetable contain hundreds of phytochemical, and these phytochemicals exhibit multiple beneficial effects in the treatment of T2DM [4].

Phenolic acids, which are part of the secondary metabolites, belong to the family of phenolic compounds and are the most common compounds in non-flavonoid group. Phenolic acids are synthesized from the shikimic acid pathway from L-phenylalanine or L-tyrosine [5]. These compounds exist predominantly as hydroxybenzoic acids, which include gallic acid, salicylic acid, protocatechuic acid, vanillic acid, and gentisic acid and hydroxycinnamic

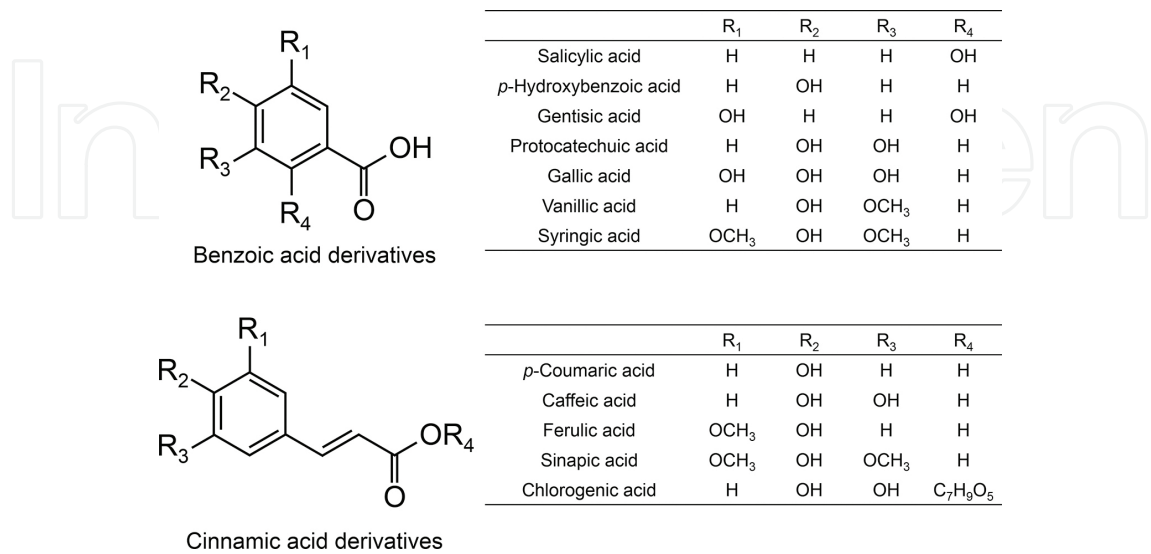


Figure 1. Chemical structures of benzoic acid and cinnamic acid derivatives.

acids, which include *p*-coumaric acid, caffeic acid, ferulic acid, sinapic acid, and chlorogenic acid (**Figure 1**). They are abundant in edible vegetable, fruits, and nuts and are the main contributors to the total polyphenol intake [6]. Although the beneficial role of phenolic acids in the lifestyle-related diseases is still controversial, reports have suggested the inverse relationship between high levels of phenolic acids intake and metabolic syndrome including T2DM [7, 8].

Because skeletal muscle is responsible for approximately 80% of insulin-mediated glucose utilization [9], it is considered that defects in insulin action on skeletal muscle are key contributors to the pathophysiology of T2DM. Studies have shown that several phenolic acids have antidiabetic effects [8], and these compounds have been implicated in the regulation of skeletal muscle glucose metabolism, especially glucose transport, a rate-limiting step for glucose utilization. However, the precise mechanism of how phenolic acids modulate glucose transport has not been firmly established. In this chapter, we provide recent experimental evidences linking phenolic acids to glucose transport and upstream signaling pathways in skeletal muscle.

2. Glucose transport in skeletal muscle

2.1. Glucose transport

Glucose transport is a major regulatory step for whole-body glucose disposal that occurs by a system of facilitated diffusion with glucose transporter (GLUT)-mediated process. GLUT is a protein of ~500 amino acids and is predicted to possess 12 transmembrane-spanning alpha helices and a single N-linked oligosaccharide. GLUT1, 3, 4, 5, 8, 10, 11, and 12 exist in mammalian skeletal muscle tissue, and especially, GLUT4 is the predominant glucose transporter isoform present in skeletal muscle. GLUT4 is present in intracellular vesicular pool in the basal non-stimulated state, and the translocation of GLUT4 from an intracellular location to the plasma membrane and T-tubules is a major determinant of acute regulation of glucose transport [10] (**Figure 2**). These glucose transport processes are regulated mainly through two different systems: insulin-dependent and insulin-independent mechanism.

2.2. Regulation of insulin-dependent glucose transport

Insulin is a peptide hormone produced by β cells of the pancreatic islets. Insulin consists of two polypeptide chains, the A and B chains, linked together by disulfide bonds. It is first synthesized as a single polypeptide called preproinsulin in pancreatic β -cells, and then it is cleaved to form a smaller protein, proinsulin. The conversion of proinsulin to insulin occurs through the combined action of the prohormone convertases [12].

The insulin receptor is a member of the ligand-activated receptor and tyrosine kinase family of transmembrane-signaling proteins that consists of two extracellular α subunits and two transmembrane β subunits connected by disulfide bridges [13]. Binding of insulin to the extracellular domain of the insulin receptor α subunit triggers tyrosine phosphorylation of the intracellular domain of the β subunit [14]. Following the autophosphorylation of the receptor,

the insulin receptor phosphorylates insulin receptor substrate (IRS)-1 on tyrosine residues. Tyrosine-phosphorylated IRS then binds to the Src homology 2 (SH2) domain-containing adaptor protein p85, a regulatory subunit of phosphatidylinositol-3 kinase (PI3K), resulting in activation of the catalytic p110 subunit of PI3K. This results in the generation of the critical second messenger PI3,4,5-triphosphate, which in turn triggers the activation of Akt. Recently, TBC1 domain family (TBC1D) member 1 (TBC1D1) and member 4 (TBC1D4) have been suggested to act as downstream mediators of Akt. TBC1D1 and TBC1D4 contain Rab GTPase-activating protein (GAP) domains that prevent GLUT4 translocation by inactivating Rab proteins. TBC1D1 and TBC1D4 dissociate from GLUT4 vesicles in the phosphorylated state and thereby facilitate GLUT4 translocation and glucose transport [15, 16] (**Figure 2**).

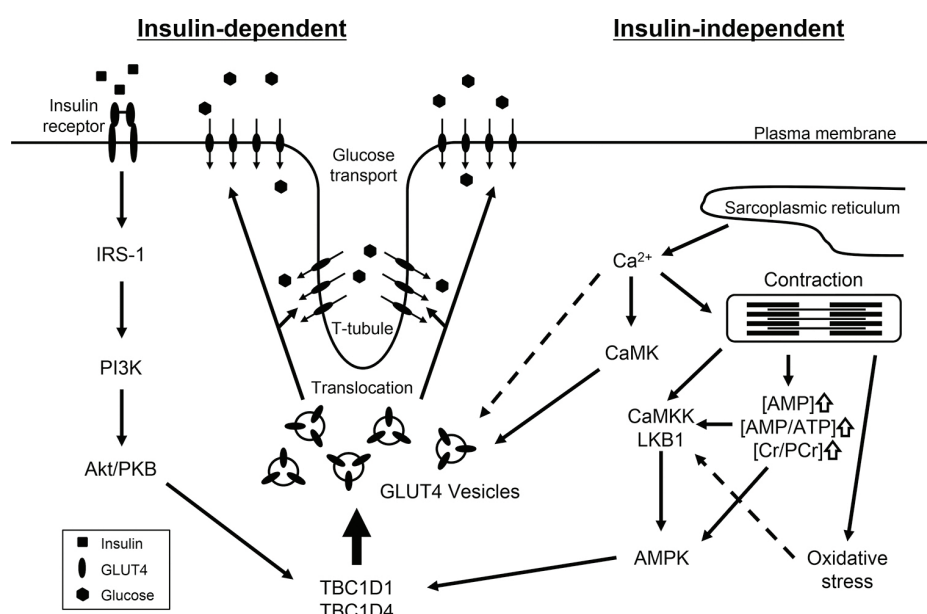


Figure 2. Molecular mechanism of stimulating insulin-dependent and insulin-independent glucose transport in skeletal muscle. This figure was adapted from Egawa et al. [11] with permission by the publisher. AMPK, 5'AMP-activated protein kinase; CaMK, Ca²⁺/calmodulin-dependent protein kinase; CaMKK, Ca²⁺/calmodulin-dependent protein kinase kinase; Cr, creatine; GLUT4, glucose transporter 4; IRS-1, insulin receptor substrate 1; LKB1, liver kinase B1; PCr, phosphocreatine; PKB, protein kinase B; PI3K, phosphatidylinositol-3 kinase; TBC1D1, TBC1 domain family member 1; TBC1D4, TBC1 domain family member 4.

2.3. Regulation of insulin-independent glucose transport

A serine/threonine protein kinase, 5'AMP-activated protein kinase (AMPK), is critical for insulin-independent glucose transport in the muscle through translocation of GLUT4. AMPK comprises a catalytic α subunit and the regulatory subunits β and γ [17] in a total of 12 possible heterotrimeric combinations of two α , two β , and three γ subunits [18]. In skeletal muscle, the predominant heterotrimeric complexes include $\alpha 1/\beta 2/\gamma 1$, $\alpha 2/\beta 2/\gamma 1$, and $\alpha 2/\beta 2/\gamma 3$ [19]. The α subunit has a catalytic domain that contains the activating phosphorylation site (Thr¹⁷²) at the N-terminus, an auto-inhibitory domain, and a conserved C-terminal domain that interacts with β and γ subunits [20–24]. There are two distinct α isoforms ($\alpha 1$ and $\alpha 2$): $\alpha 1$ is expressed

ubiquitously, whereas $\alpha 2$ is dominant in the skeletal muscle, heart, and liver [25]. The regulatory β subunit contains a C-terminal region that interacts with α and γ subunits and a central region that binds glycogen [26]. The regulatory γ subunit contains binding sites of adenine nucleotides (adenosine monophosphate (AMP), adenosine diphosphate (ADP), or adenosine triphosphate (ATP)) [18].

AMPK typically works as a signaling intermediary in muscle cells by monitoring cellular energy status, such as AMP/ATP ratio and creatine/creatine phosphate (PCr) ratio [17]. Binding of AMP to the Bateman domains of the AMPK γ subunit leads the allosteric activation of AMPK and phosphorylation of the Thr¹⁷² residue of the α subunit, which is crucial for maximal kinase activity. The level of phosphorylation also depends on the balance of activities of upstream kinases including liver kinase B1 (LKB1) and Ca²⁺/calmodulin-dependent protein kinase kinase (CaMKK) and protein phosphatases [24, 27]. The LKB1 complex is constitutively active but is not activated directly by AMP. The binding of AMP to AMPK induces a structural change that assists phosphorylation of AMPK by the LKB1 complex [28, 29]. On the other hand, CaMKK activates AMPK in response to increased intracellular Ca²⁺ levels independently of energy status [30–32].

AMPK is also activated without energy depletion by 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR), a pharmacological activator of AMPK. When taken up into skeletal muscle, AICAR is converted by adenosine kinase to ZMP, a monophosphorylated derivative that mimics the effects of AMP on AMPK [17]. AICAR-induced activation of AMPK leads to insulin-independent stimulation of glucose transport in skeletal muscle [33, 34] accompanied by GLUT4 translocation to the plasma membrane [35]. Moreover, AICAR-stimulated glucose transport is abrogated completely in muscles from mice with muscle-specific expression of a dominant-negative (kinase dead) form of AMPK [36], indicating that increased AMPK activity is sufficient for the stimulation of glucose transport in skeletal muscle.

AICAR-stimulated glucose transport is not inhibited by a PI3K inhibitor wortmannin [33], and the increase in glucose transport induced by the combination of maximal AICAR and maximal insulin stimulation is partly additive [33]. Therefore, the underlying molecular signaling mechanisms regulating insulin-dependent and insulin-independent glucose transport have been considered to be distinct. In this regard, recent studies have revealed that AMPK promotes GLUT4 translocation likely through TBC1D1 and TBC1D4 [37]. In short, insulin-dependent and insulin-independent signaling of glucose transport systems seem to converge at TBC1D1 and TBC1D4 (Figure 2).

3. Phenolic acids and glucose transport

3.1. Caffeic acid

Caffeic acid (3,4-dihydroxycinnamic acid) is the most frequently studied phenolic acids in diabetes research. A prospective investigation conducted in two cohorts of US women demonstrated that there was an inverse association between urinary excretion level of caffeic

acid and T2DM risk [38], indicating that dietary intake of caffeic acid may alleviate a development of T2DM. Indeed, several studies have shown the hypoglycemic action of caffeic acid. Intravenous injection of caffeic acid (0.5–5 mg/kg) into both streptozotocin (STZ)-induced diabetic rats and rats with insulin resistance exhibited an acute (<30 min) effect of lowering plasma glucose in a dose-dependent manner [39, 40]. Further, chronic (5–12 weeks) dietary supplementation with caffeic acid (0.02–2%) lowered blood glucose level in diabetic mice [41–43].

A previous work by us first demonstrated that incubation of isolated rat skeletal muscles with caffeic acid (0.1–1 mM) acutely (<30 min) enhanced AMPK α Thr¹⁷² phosphorylation [44, 45] (**Figure 3**). Phosphorylation of acetyl-CoA carboxylase (ACC) Ser⁷⁹ exhibited parallel changes to AMPK phosphorylation. ACC is a major substrate of AMPK in skeletal muscle, and phosphorylation of ACC at Ser⁷⁹ reflects the total AMPK activity [46–48]. Correspondingly, caffeic acid (1 mM, 30 min) stimulated insulin-independent glucose transport in skeletal muscle (**Figure 4**). Other researchers also have shown that caffeic acid enhanced insulin-independent glucose transport in isolated adipocytes [39] and cultured muscle cells [40]. Therefore, the stimulatory effect of caffeic acid on insulin-independent glucose transport may contribute to the hypoglycemic action, partly through AMPK-mediated mechanism.

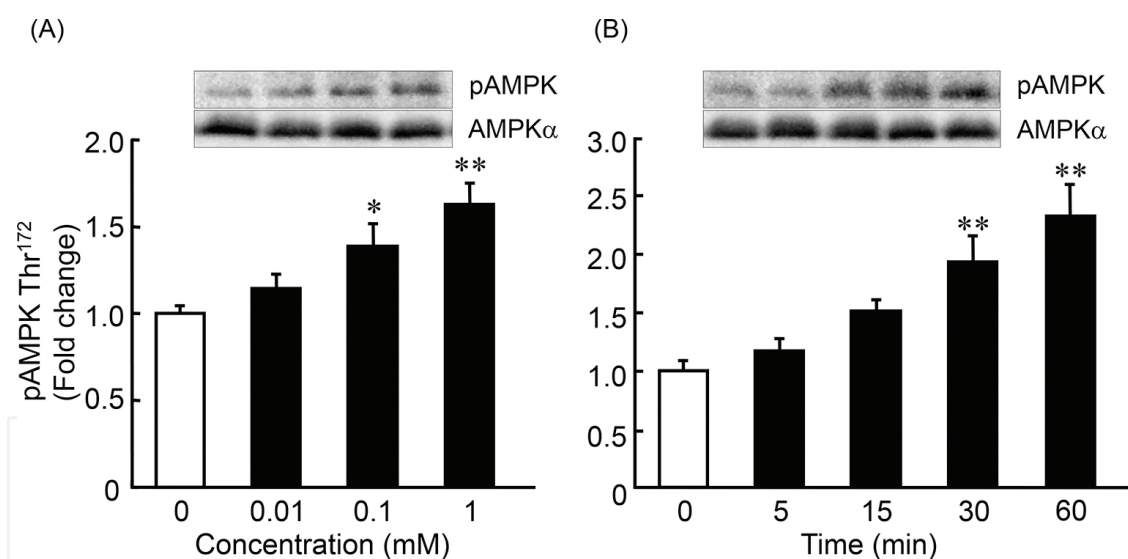


Figure 3. The effect of caffeic acid on phosphorylation status of AMPK α Thr¹⁷² in skeletal muscle. (A) Isolated epitrochlearis muscles were incubated with caffeic acid at indicated concentration for 30 min. (B) Isolated epitrochlearis muscles were incubated with caffeic acid (1 mM) at indicated time. Muscle lysates were then analyzed for phosphorylation of AMPK α Thr¹⁷² (pAMPK) by western blot analysis. Fold increases are expressed relative to the level of muscles in the non-stimulated group. Representative immunoblots are shown. Values are mean \pm SE. * P < 0.05, ** P < 0.01 vs. non-stimulated group. This figure was adapted from Tsuda et al. [44] with permission by the publisher.

The finding that caffeic acid enhances phosphorylation status of AMPK α Thr¹⁷² indicates that caffeic acid leads to covalent modification through upstream kinases. Since the binding of AMP to AMPK facilitates the phosphorylation of AMPK by the LKB1 complex [28], LKB1 is considered as a crucial AMPK kinase in response to energy depletion in skeletal muscle. When

cellular ATP level is depleted, phosphate is transferred from PCr to ADP to reproduce ATP. Decreased PCr level leads to an increase in free ADP and thereby causes AMP accumulation through the reaction of adenylate kinase, and thus a reduction of PCr level indicates a cellular energy depletion. In our previous work [44], we observed that incubation of rat skeletal muscles with caffeic acid decreased PCr level, suggesting that LKB1 is a possible kinase to enhance the caffeic acid-induced AMPK α Thr¹⁷² phosphorylation.

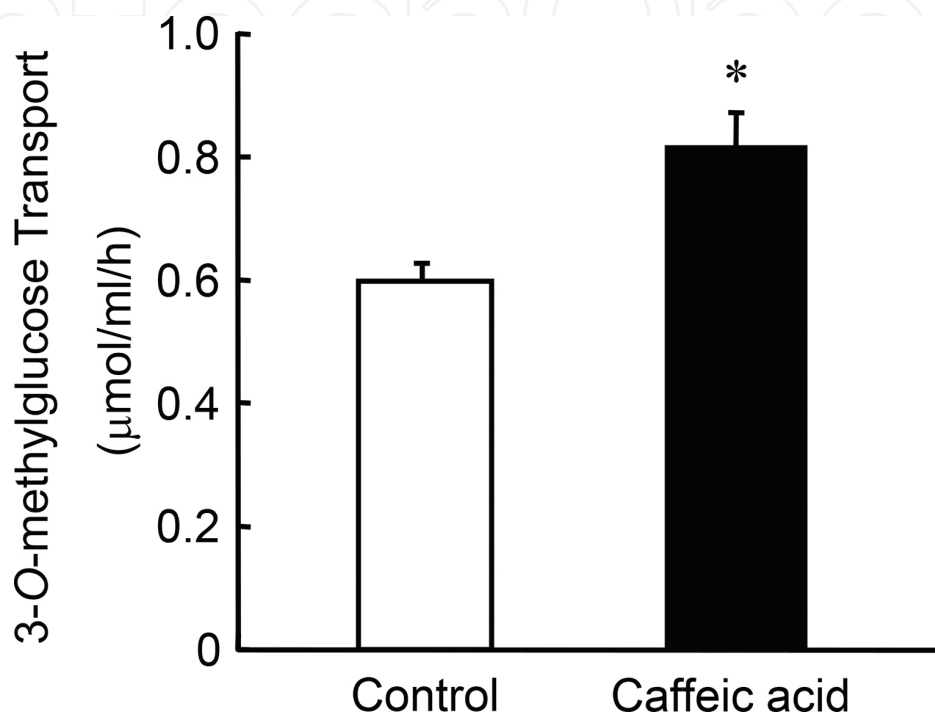


Figure 4. The effect of caffeic acid on insulin-independent glucose transport in rat skeletal muscles. Isolated epitrochlearis muscles were incubated in the absence (control) or presence of 1 mM caffeic acid for 30 min, and then glucose transport activity was measured using the glucose analog 3-O-methylglucose. Values are mean \pm SE. * $P < 0.05$ vs. control. This figure was adapted from Tsuda et al. [44] with permission by the publisher.

Exercise (muscle contraction) is a strong stimulator for insulin-independent glucose transport. Due to the provision of energy for contracting muscle during exercise, AMP and ADP levels are rapidly increased in an intensity-dependent manner while ATP levels decline slightly. Since AMPK is a sensor of cellular energy status that is activated by AMP/ATP ratio, AMPK is activated during exercise in an intensity-dependent manner [49–52]. Thus, exercise can regulate insulin-independent glucose transport by a mechanism involving AMPK [33]. Recent work by us showed an interesting finding that muscle contraction and caffeine, which is the most widely consumed phytoactive substance in the world, synergistically stimulate insulin-independent glucose transport and AMPK Thr¹⁷² phosphorylation in skeletal muscle [45]. This result indicates the possibility that some phytochemicals enhance the maximal capacity of contraction-induced AMPK activity in skeletal muscle. In the point of view, we evaluated the effect of caffeic acid on contraction-stimulated AMPK activity in skeletal muscle. Maximal activation of AMPK by contraction was induced by 10 min tetanic contraction according to the protocol by Musi et al. [52]. AMPK α Thr¹⁷² phosphorylation was increased in response to caffeic

acid (1 mM, 30 min) stimulation; however, caffeic acid had no effect on the contraction-stimulated AMPK α Thr¹⁷² phosphorylation [45]. This finding suggests that caffeic acid has no capacity for enhancing contraction-induced AMPK activity.

It seems that caffeic acid stimulates insulin-dependent glucose transport at insulin resistance state in skeletal muscle. Insulin resistance is in which there are impaired biological and physiological responses to insulin in the tissue, and skeletal muscle insulin resistance is a major factor in the pathogenesis of T2DM. The underlying cellular mechanisms are yet unclear, but tumor necrosis factor α (TNF α), which is a member of the TNF ligand superfamily and a multifunctional cytokine, is implicated in the development of insulin resistance [53]. Activation of the TNF receptor results in stimulation of nuclear factor- κ B (NF- κ B) signaling via inhibitor κ B kinase (IKK). IKK is the master regulator of NF- κ B activation in response to inflammatory stimuli, and the IKK/NF- κ B pathway is considered to be a core mechanism that causes insulin resistance in peripheral tissues including skeletal muscle [54, 55]. We demonstrated that, during insulin-stimulated condition, caffeine-induced insulin resistance which includes activation of IKK/NF- κ B signaling and suppression of Akt Ser⁴⁷³ phosphorylation, which is required for the full activation of Akt, and insulin-dependent glucose transport, were alleviated by the treatment with caffeic acid in rat skeletal muscle [56]. Hence, caffeic acid may have an ability to improve insulin resistance state that is induced by activation of IKK/NF- κ B signaling. Notably, caffeic acid does not stimulate insulin signaling pathway in normal state because we have shown that incubation of isolated rat skeletal muscle with caffeic acid had no effect on stimulating Akt Ser⁴⁷³ phosphorylation in the basal condition [44, 45].

3.2. Chlorogenic acid

Chlorogenic acid is the ester of caffeic acid and (–)-quinic acid and has been implicated in reducing the risk of T2DM. In animal study, treatment of chlorogenic acid (250 mg/kg) acutely (<30 min) lowered blood glucose concentration during glucose tolerance test in diabetic db/db mice [57, 58]. Furthermore, repeated (2–12 weeks) treatment of chlorogenic acid (80–250 mg/kg/day) improved fasting blood glucose concentration, HOMA-IR index (fasting insulin [μ U/ml] \times fasting glucose [mmol/l]/22.5), blood glucose concentration during glucose or insulin tolerance test in db/db mice [58, 59], and high-fat diet-induced diabetic mice [60]. Intervention with lower doses of chlorogenic acid (5 mg/kg/day) also improved the peak blood glucose concentration during glucose tolerance test in Zucker (fa/fa) rats although fasting blood glucose concentration did not change [61]. In human study, chlorogenic acid ingestion (1 g) reduced blood glucose concentration during oral glucose tolerance test in overweight men [62]. Thus, the accumulated evidences strongly suggest that chlorogenic acid has a hypoglycemic effect, but the cellular mechanism of action is not fully understood yet.

Stimulatory effect of chlorogenic acid on skeletal muscle glucose transport was firstly reported by Prabhakar and Doble [63]. They revealed that incubation with chlorogenic acid (25 μ M) stimulated insulin-independent glucose transport within 3 h in differentiated L6 skeletal muscle cells. Subsequently, Ong et al. [57] demonstrated that incubation of isolated skeletal muscle from db/db mice and L6 skeletal muscle cells with chlorogenic acid (1–10 mM) for 1–24 h enhanced insulin-independent glucose transport. They also showed that

chlorogenic acid-stimulated glucose transport was inhibited by the pretreatment with compound C, an AMPK inhibitor, but not wortmannin, a PI3K inhibitor. These findings suggest that chlorogenic acid stimulates skeletal muscle glucose transport via insulin-independent and AMPK-dependent mechanism.

The previous work by us investigated the acute effect of chlorogenic acid on AMPK α Thr¹⁷² phosphorylation status in rat skeletal muscle [44] and showed that incubation with chlorogenic acid (<1 mM, <60 min) had no effect on AMPK α Thr¹⁷² phosphorylation in isolated rat skeletal muscle. In contrast, Ong et al. [57] demonstrated that chlorogenic acid had an ability to enhancing AMPK activity in L6 skeletal muscle cells in dose-dependent (1–10 mM) and time-dependent (1–24 h) manners. These findings suggest that chlorogenic acid directly acts skeletal muscle and stimulates AMPK, and that relatively higher concentration of chlorogenic acid (>1 mM) and/or longer stimulation period (>60 min) is needed to stimulate skeletal muscle AMPK.

Adiponectin is an adipokine that has been recognized as a key regulator of glucose metabolism. Binding of adiponectin to adiponectin receptor AdipoR1 induces Ca²⁺ influx and leads to the activation of CaMKK/AMPK signaling in skeletal muscle [64]. A study showed that AMPK α Thr¹⁷² phosphorylation and ACC Ser⁷⁹ phosphorylation were upregulated in response to chronic (2 weeks) administration of chlorogenic acid (250 mg/kg/day) in skeletal muscle of db/db mice [58]. In addition, the treatment also increased CaMKK expression in skeletal muscle. More recently, Jin et al. [59] showed that treatment with chlorogenic acid (80 mg/kg/day) for 12 weeks increased AMPK α Thr¹⁷² phosphorylation as well as AdipoR1 expression in skeletal muscle of db/db mice. Collectively, chronic treatment of chlorogenic acid may act as an antidiabetic agent through stimulating adiponectin-AMPK signaling because AMPK induces a variety of metabolic changes toward antidiabetic property: promoting glucose transport [33, 34, 36, 65], GLUT4 expression [66–68], fatty acid oxidation [49, 69, 70], mitochondrial biogenesis [71, 72], insulin sensitivity [73, 74], and fiber-type shift toward the slower and more oxidative phenotype [75].

Notably, chlorogenic acid is hydrolyzed by intestinal microflora into various aromatic acid metabolites including caffeic and quinic acids [76]. Additionally, it is reported that absorption rate of caffeic acid in the small intestine of humans is 95% but chlorogenic acid is 33% [77]. These observations suggest that the health-promoting effects of chlorogenic acid might be attributed to the actions of chlorogenic acid-derived caffeic acid. In this context, the stimulatory effect of oral intake of chlorogenic acid as well as caffeic acid at physiological doses on AMPK activation and AMPK-related metabolic events, including glucose transport in skeletal muscle, must be confirmed.

3.3. Gallic acid

Gallic acid (3,4,5-trihydroxybenzoic acid) is known to have a variety of cellular functions including beneficial effects on T2DM. Chronic treatment (4–16 weeks) with gallic acid (25–100 mg/kg/day) produced significant decrease in elevated fasting serum glucose level in STZ-induced diabetic rats [78], in high-fat diet-induced diabetic mice [79], or in high-fat diet/STZ-induced diabetic rats [80, 81]. Four weeks of treatment with gallic acid (10–30 mg/kg/day) in

high-fructose diet-induced diabetic rats also ameliorates hyperglycemia and HOMA-IR index and improved glucose clearance during oral glucose tolerance test [82].

A study reported that treatment with gallic acid (10 μ M) for 30 min induces GLUT4 translocation and insulin-independent glucose transport in 3T3-L1 adipocytes [83]. We found that a water-soluble Pu-erh tea extract which contained 9.11% gallic acid stimulated Akt Ser⁴⁷³ phosphorylation in a dose- and time-dependent manner with a concomitant increase in insulin-independent glucose transport in isolated rat skeletal muscle [84]. By contract, the Pu-erh tea extract did not change the phosphorylation status of AMPK α Thr¹⁷². Correspondingly, incubation of isolated rat skeletal muscle with gallic acid (820 μ M) for 30 min robustly stimulated Akt Ser⁴⁷³ phosphorylation without affecting AMPK phosphorylation [84] (**Figure 5**). These findings indicate that gallic acid stimulates glucose transport via enhancing insulin signaling transduction in the absence of insulin and raise the possibility that gallic acid can be an insulin-mimetic agent.

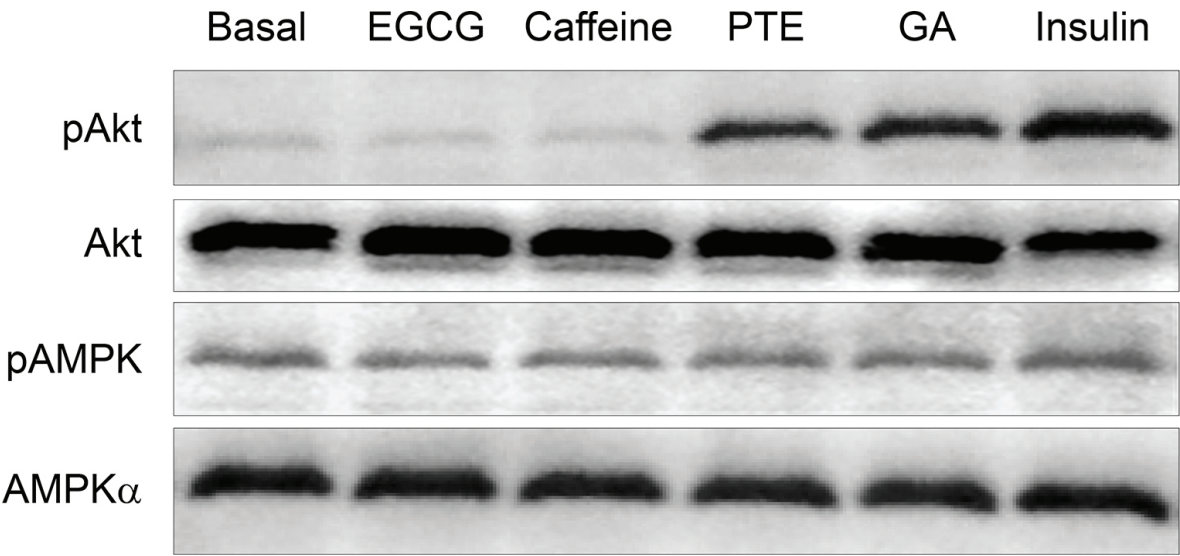


Figure 5. The effect of gallic acid (GA) on phosphorylation status of Akt Ser⁴⁷³ and AMPK α Thr¹⁷² in skeletal muscle. Isolated epitrochlearis muscles were incubated in the absence (Basal) or presence of epigallocatechin gallate (EGCG) (2.2 μ M), caffeine (150 μ M), Pu-erh tea hot-water extract (PTE) (1.5 mg/mL), GA (820 μ M), or insulin (1 μ M) for 30 min. The concentrations of GA, caffeine, and EGCG were adjusted to the concentration of each constituent to the level corresponding to 1.5 mg/mL of PTE. Muscle lysates were then analyzed for phosphorylation of Akt Ser⁴⁷³ (pAkt) and AMPK α Thr¹⁷² (pAMPK) by western blot analysis. Representative immunoblots are shown. This figure was adapted from Ma et al. with permission by the publisher.

3.4. Salicylic acid

Salicylic acid (salicylate or 2-hydroxybenzoic acid) is one of the oldest drugs in clinical practice. Salicylate has been used for treating pain, fever, and inflammation, but recent evidences have accumulated the effectiveness of treating T2DM. Over 100 years ago, Ebstein [85] and Williamson [86] showed that high doses of sodium salicylate (5–7.5 g/day) reduced glucosuria in diabetic patients. After that, additional trials have been reported similar effects that the treatment of sodium salicylate improved glucose homeostasis [87–94]. A recent meta-analysis

of salicylates, including sodium salicylate, aspirin (acetylsalicylate), and salsalate (2-[2-hydroxybenzoyl]oxybenzoic acid), for T2DM showed that any doses of salicylates reduce glycated hemoglobin (HbA1c) level and that high doses of sodium salicylate (>3000 mg/day) improve fasting plasma glucose level [95].

The mechanism of antidiabetic action of salicylate might be attributed to the stimulation of both insulin-dependent and insulin-independent glucose transport. Kim et al. [96] demonstrated that infusion of lipid into tail vein of rats for 5 h impaired insulin-dependent glucose transport in skeletal muscle, whereas the impairment was attenuated by concomitant infusion of sodium salicylate (7 mg/kg/h). In that situation, the decreases in insulin-dependent glucose transport in skeletal muscle were associated with the reduction of tyrosine phosphorylation of IRS-1 and PI3K activity [96]. Salicylate is a known inhibitor of IKK/NF- κ B signaling. Kim et al. [96] also revealed that the defects of insulin-dependent glucose transport with lipid infusion were not induced in IKK- β knockout mice. Overall, these results indicate that salicylate may protect the defects of fat-induced insulin resistance in skeletal muscle by preserving insulin signaling transduction via the inhibition of IKK/NF- κ B signaling.

Recent work by us first showed that the treatment of sodium salicylate (5 mM, 30 min) stimulated insulin-independent glucose transport in rat-isolated skeletal muscles [97]. The stimulation of insulin-independent glucose transport by sodium salicylate may be explained by the activation of AMPK. A study found that sodium salicylate (>1 mM) activates AMPK in human embryonic kidney cells directly by binding to AMPK (1–10 mM) and indirectly by energy depletion (>10 mM) [98]. In addition, we showed that incubation of isolated rat skeletal muscles with sodium salicylate (>5 mM) increased AMPK α Thr¹⁷² phosphorylation and AMPK activity accompanied by the reduction of energy status (ATP, PCr, and glycogen) [97]. The depletion of energy levels in response to sodium salicylate stimulation was also observed in *Drosophila* tissue culture (SL2) cells [99] and neutrophils [100]. Inhibition of oxidative phosphorylation by sodium salicylate was suggested to cause to energy depletion [101]. These findings suggest that salicylate stimulates AMPK via both energy-dependent and energy-independent processes in skeletal muscle. It seems that CaMKK signaling is not involved in salicylate-induced AMPK activation because the CaMKK inhibitor STO-609 had no effect on responses to salicylate [98].

3.5. *p*-Coumaric acid

p-Coumaric acid (4-hydroxycinnamic acid) is the precursor of caffeic acid and has potential to reduce the risk of T2DM. Some studies showed that chronic (30–45 days) treatment with *p*-coumaric acid improved fasting blood glucose and HbA1c levels in STZ-induced diabetic rats [102–104]. In addition, a study demonstrated that *p*-coumaric acid stimulated insulin-independent glucose transport and AMPK α Thr¹⁷² phosphorylation in L6 skeletal muscle cells and that the upregulation of glucose transport was partially attenuated by concomitant treatment with AMPK inhibitor compound C [105]. This finding indicates that *p*-coumaric acid stimulates insulin-independent glucose transport via AMPK-activation in skeletal muscle.

3.6. Ferulic acid

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is derived from the biosynthesis of caffeic acid and has antidiabetic effects. Chronic treatment with ferulic acid showed a hypoglycemic effect in diabetic mice [106–108]. A study reported that ferulic acid stimulated insulin-independent glucose transport in L6 skeletal muscle cells in a dose-dependent ($<50\ \mu\text{M}$) and time-dependent ($<5\ \text{h}$) manners [63]. In contrast, another study showed that treatment with ferulic acid ($250\text{--}500\ \mu\text{M}$) inhibited insulin-independent glucose transport in L6 skeletal muscle cells [109]. Therefore, further studies are needed to clear the effect of ferulic acid on glucose transport system.

3.7. Sinapic acid

Sinapic acid (sinapinic acid or 4-hydroxy-3,5-dimethoxycinnamic acid) is known to have an anti-inflammatory action through NF- κ B inactivation [110]. Inflammation links with the progress of T2DM, and thus, it is indicated the merit of sinapic acid in the treatment of T2DM. Indeed, a single administration of sinapic acid ($10\text{--}30\ \text{mg/kg}$) dose-dependently reduced the hyperglycemia of STZ-induced diabetic rats [111, 112]. Further, sinapic acid ($0.1\text{--}10\ \mu\text{M}$) stimulated enhanced insulin-independent glucose transport in isolated rat skeletal muscle and L6 skeletal muscle cells [112]. Repeated treatment with sinapic acid ($25\ \text{mg/kg}$) for 3 days increased the gene expression of GLUT4 in skeletal muscle of STZ-induced diabetic rats [112]. Considering that AMPK promotes GLUT4 expression [66–68], sinapic acid-induced stimulation of glucose transport and GLUT4 expression may be mediated by AMPK activation.

4. Conclusion

Phytomedicine is becoming to be an important medical treatment, and thus it is necessary to understand the molecular mechanism underlying the effectiveness of phytochemicals on health promotion. In this chapter, we reviewed the relationship between phenolic acids and T2DM focusing on skeletal muscle glucose transport systems. Among many phenolic acids, it has been reported that caffeic acid, chlorogenic acid, gallic acid, salicylic acid, *p*-coumaric acid, and sinapic acid stimulate glucose transport in skeletal muscle (**Table 1**). AMPK appears to be involved in these glucose utilization processes. Caffeic acid, chlorogenic acid, salicylic acid, and *p*-coumaric acid seem to have capacity for stimulating AMPK activity, thereby enhancing insulin-independent glucose transport. On the other hand, gallic acid has no effect on AMPK activity but stimulates insulin signaling without insulin. Caffeic acid and salicylic acid may also enhance insulin sensitivity by suppressing IKK/NF- κ B signaling.

Physical exercise is a powerful tool that promotes good health, and it reduces the risk of T2DM. Skeletal muscle AMPK is considered to be a candidate therapeutic target molecule in T2DM since AMPK is activated by physical exercise. If skeletal muscle AMPK could be activated by alternative approaches including phytochemicals, it would benefit people who are unable to engage in physical exercise. As described above, caffeic acid has no capacity for enhancing contraction-induced AMPK activity. This finding suggests that caffeic acid may not strengthen

the exercise benefit but simultaneously means that caffeic acid and contraction have a common mechanism to stimulating insulin-independent glucose transport through AMPK. Therefore, caffeic acid has a potential as an exercise-mimetic stimulator for glucose transport systems. Thus, we expect that some kinds of phytochemicals have potential to act as preventive and therapeutic agents for T2DM.

Phenolic acids	Insulin-dependent glucose transport	Insulin-independent glucose transport	Molecular responses
Caffeic acid	↑ (insulin resistance state)	↑	AMPK activity ↑, Energy status ↓, NF-κB activity ↓
Chlorogenic acid	—	↑	AMPK activity ↑ (>1 mM, >60 min) AMPK expression ↑, CaMKK expression ↑
Gallic acid	—	↑	Akt activity ↑, AMPK activity →
Salicylic acid	↑ (lipid infused state)	↑	Insulin-stimulated IRS-1 tyrosine phosphorylation ↑, Insulin-stimulated PI3K activity ↑ NF-κB activity ↓, AMPK activity ↑ Energy status ↓, CaMKK activity →
<i>p</i> -Coumaric acid	—	↑	AMPK activity ↑
Ferulic acid	—	↑	—
Synapic acid	—	↑	GLUT4 gene expression ↑

AMPK, 5'AMP-activated protein kinase; CaMKK, Ca²⁺/calmodulin-dependent protein kinase kinase; GLUT4, glucose transporter 4; IRS-1, insulin receptor substrate 1; NF-κB, nuclear factor-κB; PI3K, phosphatidylinositol-3 kinase; ↑, increase; ↓, decrease; →, no change; —, no study.

Table 1. Summary of the effect of phenolic acids on skeletal muscle glucose transport.

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