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The polypharmacy reduction potential of cinnamic acids and some related compounds in pre- and post-onset management of type 2 diabetes mellitus

Douglas Edward Barre, Kazimiera Amelia Mizier-Barre

Department of Health Sciences, Cape Breton University, Sydney, Nova Scotia, Canada
E-mail: ed_barre@cbu.ca

Objectives. This review assesses the polypharmacy reduction potential of cinnamic acids (CAs) and some related compounds in managing three or more of the cluster of seven, pre- and post-type 2 diabetes mellitus (T2DM)-related features (central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation, and inflammation).

Methods. Google scholar and Pubmed were searched for cinnam*, chlorogenic acid, ferulic acid, and caffeic acid in conjunction with each of pre- and post-onset T2DM, central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation, and inflammation. The study was divided into an introduction followed by findings on the impacts of each of the CAs including trans-CA acid, the E isomer of a CA-based thiazolidinedione and a metabolite of that isomer, as well as p-methoxy CA, various cinnamic amides and some other CA-related compounds (chlorogenic acid, cinnamaldehyde, ferulic and caffeic acid).

Results. Trans-CA has a potential to manage three, while each of chlorogenic acid, cinnamaldehyde, caffeic acid and ferulic acid has a potential to manage all seven members of the cluster. Other CA-related compounds identified may manage only one or two of the cluster of seven.

Conclusions. Much of the work has been done in animal models of pre- and post-onset T2DM and non-pre- or post-onset T2DM humans and animals, along with some cell culture and in vitro work. Very little work has been done with human pre- and post-onset T2DM. While there is potential for managing 3 or more members of the cluster with many of these compounds, a definitive answer awaits large pre- and post-T2DM onset clinical trials with humans.

Key words: cinnamic acids and related compounds, type 2 diabetes mellitus, central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation

Central obesity is frequently a start of the cascade of events leading to a cluster of hyperglycemia, hypertension, dyslipidemia (most often decreased plasma/serum high density lipoprotein cholesterol (HDLc) and increased triglycerides, but also sometimes increased cholesterol and low density lipoprotein cholesterol (LDLc)), pro-thrombosis, increased oxidation including that of LDL and subsequent inflammation, all of which frequently lead to or are the part of type 2 diabetes mellitus (T2DM) (Steinberg 1992; Erkelens 2001; Beckman et al. 2002; Gresele et al. 2003; Carr and Brunzell 2004; Krauss 2004; Dandona et al. 2005; Avogaro et al. 2006; Boudjeltia et al. 2006; Grundy 2006a,b; Wright et al. 2006; Azuma et al. 2007; Devaraj et al. 2007). In addition, the sequential pathway, if unchecked, leads to a progressive spiraling of loss of glycemic control (Dandona et al. 2005). The search for new agents to combat three or more of the seven features contributing to and/or being part of T2DM post-onset continues as numerous problems

Corresponding author: Dr. Douglas Edward Barre, Department of Health Sciences, Cape Breton University, Sydney, Nova Scotia, Canada, B1P 6L2; phone: 902-563-1921; fax: 902-563-1945; e-mail: ed_barre@cbu.ca.

with polypharmacy have been reported (Austin 2006; van Bruggen et al. 2009; Dunn 2010; Huang et al. 2010). Grundy (2006a,b) has suggested a single drug or single combination of drugs would be helpful in pre- and post-onset T2DM managed by polypharmacy reduction.

The E isomer of a CA-based thiazolidinedione and a metabolite of that isomer as well as p-methoxy CA, various cinnamic amides, chlorogenic acid, cinnamaldehyde, ferulic and caffeic acids are compounds in this family that have received the most attention. However, a review of the literature in terms of the potential of CAs and some of their related compounds to combat the cluster of seven has not been done and so it is important to assess whether such potential exists.

The purpose of this review is to discuss evidence or note lack thereof for the use of CAs and some of their related compounds in polypharmacy reduction in terms of safely and efficaciously combatting three or more members of the aforementioned seven features in both pre- and post-T2DM onset in the short and long term.

Impact of CAs and some of their related compounds on the cluster of seven and T2DM

It appears that there are not available any reports on the impact of CAs on central obesity in terms of prevention or post-onset management in humans, but in high fat diet fed rats an unspecified CA reduced the extent of weight gain (Mnafgui et al. 2015). Barre et al. (2012) have found that consumption of flaxseed lignan complex (FLC) containing unspecified CAs also diminished waist circumference gain though such results cannot be unquestionably assigned to the CAs as other compounds were in the FLC. Cinnamaldehyde lowered body weight in db/db mice (a T2DM model) (Li et al. 2012), but it is not clear if that is represented by a fat mass reduction. Similarly, Huang et al. (2011) have found that cinnamaldehyde administration to high fat diet fed Institute of Cancer Research (ICR) mice resulted in slower weight gains but again, there was no specific indication of fat mass gain reduction though they were able to show cinnamaldehyde-induced lipid accumulation reduction in 3T3 L1 differentiated adipocytes. Along those lines, Khare et al. (2016) have observed reduced lipid accumulation in mature adipocytes after cinnamaldehyde was incubated with 3T3 L1 pre-adipocytes. The reduced lipid accumulation was due, at least in part, to a shift toward lipolysis. Khare et al. (2016) have also noted a cinnamaldehyde decrease in weight in high fat fed Swiss male albino mice due at least in part to a decreased serum leptin:ghrelin ratio. Such a combination of these hormones reduced weight regain in a group of overweight and obese humans (Crujeiras et al. 2014). Thus, cinnamaldehyde may be important in weight management and reducing adipose tissue lipid accumulation hence reducing the risk of T2DM. Ferulic acid suppressed obesity and visceral fat accumulation (de Melo et al 2017) and hepatic fat (Wang et al. 2018) in high fat diet-induced obese mice.

Chlorogenic acid is poorly absorbed (1/3 across the small intestinal wall in humans (Olthof et al. 2001; Gonthier et al. 2006) due to its quinic acid group (chlorogenic acid is derived from the esterification of quinic acid to caffeic acid). However, chlorogenic acid can be metabolized by the human microbiome to caffeic acid among other metabolites (Gonthier et al. 2006; Bel-Rhlid et al. 2013; Tomas-Barberan et al. 2014). Yet, Del Rio et al. (2010) have indicated that most of the catabolism of chlorogenic acid to caffeic acid occurs at the small intestine. Indeed, Del Rio et al. (2010) have pointed out that most of the absorption of caffeic and ferulic acid also occurs at the small intestine with some absorption also occurring at the colon. The findings of Del Rio et al. (2010) have stood in sharp contrast to Plumb et al. (1999) who have posited that all of the chlorogenic acid esterase activity was in the microbiome of the large intestine. However, Plumb et al. (1999) did tissue extract work rather than the more reliable *in vivo* work of Del Rio et al. (2010) who have compared humans with ileostomies to those with intact colons. Regardless, the important outcome is the chlorogenic acid esterase activity and not its location as chlorogenic acid metabolites contribute to management of the cluster of seven along with chlorogenic acid. Chlorogenic acid administered in a double-blind randomized placebo-controlled study to impaired glucose tolerance patients for 12 weeks resulted in mild waist circumference reduction (Zuniga et al. 2018). Meng et al. (2013) in a review paper indicated that chlorogenic acid could suppress weight gain in mice, while Bhandarkar et al. (2019) have found that chlorogenic acid consumption reduced energy intake, waist circumference, and visceral adiposity in rats fed a high carbohydrate, high fat diet. Cho et al. (2010) have found reduced body weight, visceral fat mass, and plasma leptin due to each of chlorogenic acid and caffeic acid intake in high fat diet-induced obesity in mice. Park et al. (2017) have noted in humans that chlorogenic acid increased fat oxidation during sleep and thus could control obesity. Whether it is chlorogenic acid and/or caffeic acid that contributes to these outcomes is not clear.

Adisakwattana (2017) has noted that CA and their derivatives have glucose management potential in humans via different mechanisms that include increased insulin secretion, better pancreatic β-cell function, hepatic gluconeogenesis inhibition, better glucose uptake, strengthened post-insulin binding intracellular signaling mechanisms, delayed carbohydrate digestion and absorption, and decreased protein glycation and insulin fibrillation. Various CAs have been identified as alpha-glucosidase inhibitors (Adisakwattana et al. 2004, 2009), which have the potential to lower blood plasma glucose levels via delayed small intestinal carbohydrate digestion (Caspary 1978; Caspary and Graf 1979). Hafizur et al. (2015) have found that trans-CA improved glucose tolerance in vivo in streptozotocin-induced T2DM rats and increased insulin secretion in isolated mice islets. Interestingly, a CA-based thiazolidinedione decreased serum glucose in db/db mice (Arlt et al. 2004). Along those lines of thought, Neogi et al. (2003) have found that the E-isomer of a CA-based thiazolidinedione, and a metabolite of that compound, lowered blood glucose in ob/ob mice (a cell culture study using HEK293 cells done by these authors as part of the same study suggested PPARγ activation as a mode of action for these two agents). Furthermore, Yoo et al. (2012) have found that an intraperitoneal dose of 150 mg/kg body weight/day of an unspecified CA decreased fasting blood glucose levels in db/db T2DM model mice. Lowering of fasting blood glucose in non-obese T2DM rats consuming CA occurs in a manner comparable to the sulphonylurea, glibenclamide; as well CA increased glucose-stimulated insulin secretion from isolated pancreatic islets as noted in a review paper (Cicero and Colletti 2016). Wang et al. (2015) have observed that trans-CA lowered serum glucose in alloxan-induced T2DM in rats and indicated that increased insulin secretion and activation of Glut-4 may be the explanation for such. As well Kopp et al. (2014) have noted trans-CA increased adiponectin secretion by 3T3-L1 adipocytes, and in these cells, phosphorylation of adenosine monophosphate activated protein kinase (AMPK)-activated protein kinase via G-protein-coupled receptor signaling; adiponectin and phosphorylation of AMPK-activated via G-protein-coupled receptor increases glucose uptake (Kadowaki and Yamauchi 2005). Lakshmi et al. (2009) have found that GLUT-4 mRNA expression was increased in L6 myotubes exposed to an unspecified CA [GLUT-4 is essential to the uptake of glucose by skeletal muscle cells (L6 myotubes are derived from rat skeletal muscle)]. The above-mentioned observations may be consistent with the findings of Barre et al. (2012) who have found that with FLC (containing unspecified CAs) administration to T2DM patients, there was lower fasting plasma glucose; however, such results may have been due to other FLC components. In addition, chlorogenic acid inhibits pancreatic α-amylase *in vitro*, a contributor to small intestinal carbohydrate digestion and hence blood glucose levels (Funke and Melzig 2006). Huang et al. (2009), using a non-specified CA and one of its related compounds, caffeic acid, have found that they improved glucose uptake in TNF-α induced insulin-resistant mouse hepatocytes while Adisakwattana et al. (2005, 2008) have found that p-methoxyCA and other CA related compounds increased plasma insulin and decreased plasma glucose in normal and streptozotocin-induced T2DM rats. Adisakwattana et al. (2005) have suggested that p-methoxyCA administered to streptozotocin-induced T2DM rats increased insulin secretion and glycolysis and decreased gluconeogenesis, all of which are important in lowering plasma glucose concentrations.

Madsen and Westergaard (2001), in a review, have found potential for hyperglycemia reduction in that chlorogenic acid is an *in vitro* inhibitor of glucose-6-phosphatase; such inhibition contributes to reduced glycogen breakdown and hence ultimately decreased hepatic glucose release into plasma. In a review paper, Meng et al. (2013) have indicated that chlorogenic acid could be used for improved glucose control; suggested mechanisms included α-glucosidase inhibition, elevated AMPK (an energy level sensor gauge and energy balance regulator) (Kahn et al. 2005), which increases GLUT-4 glucose capture in certain cells (supported in rat skeletal muscle (Kurth-Kraczek et al. 1999), isolated soleus muscle from diabetic mice (increased glucose uptake) and in cultured L6 myotubes (AMPK mediated GLUT-4 glucose capture) (Ong et al. 2012). Inhibition of hepatic glucose-6-phosphatase in db/db mice fed chlorogenic acid was also noted by Meng et al. (2013). Such inhibition decreases gluconeogenesis and hence glucose release into the blood (Ong et al. 2013). Van Dijk et al. (2009) have found that consumption of 1 g of chlorogenic acid 30 min before an oral glucose tolerance test in 15 overweight men resulted in lower glucose and insulin concentrations at 15 min after the consumption of glucose. Consistent with this is that chlorogenic acid administered to impaired glucose tolerance patients for 12 weeks resulted in better fasting plasma glucose concentration and an insulinogenic index reduction compared to baseline in the chlorogenic acid group (no changes in these parameters occurred in the placebo group) (Zuniga et al. 2018). Cho et al. (2010) have observed decreased

plasma insulin concentrations due to each of chlorogenic acid and caffeic acid intake in high fat diet-induced obesity in mice suggesting their potential for hyperglycemia management. However, Nyambe-Silavwe and Williamson (2018) have found chlorogenic acid to be a weak *in vitro* inhibitor of human salivary α-amylase, relative to Acarbose; human salivary α-amylase is a contributor to the availability of glucose for intestinal absorption and hence blood glucose control. Caffeic acid and chlorogenic acid inhibit α-amylase and α-glucosidase *in vitro*, each of which contribute to the rise of free glucose available of intestinal absorption thus helping to manage plasma glucose concentrations (Oboh et al. 2015). Of these caffeic acid was better at inhibiting α-amylase (consistent with Nyambe-Silavwe and Williamson 2018) and α-glucosidase (Oboh et al. 2015). Regrettably, neither caffeic nor chlorogenic acids have be tested *in vivo* in humans regarding α-amylase and α-glucosidase activity modulation so their effectiveness in managing human blood glucose levels via inhibition of these two enzymes remains unknown. Jung et al. (2006) have noted a decrease in fasting blood glucose in db/db mice receiving caffeic acid in part due to increased adipose Glut-4 expression and decreased hepatic glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities.

Ferulic acid decreased blood glucose in db/db mice (Jung et al. 2007) associated with increased plasma insulin and increased hepatic glycogen synthesis. Jung et al. (2007) have also noted that ferulic acid inhibited baker's yeast α-glucosidase *in vitro* (unfortunately the potential of ferulic acid's inhibition of human α-glucosidase by humans has apparently not been assessed). Devi et al. (2018) have proposed, via molecular docking studies, that ferulic acid can inhibit glycogen synthase kinase-3 (GSK-3). GSK-3 is an inhibitor of glycogen synthase (GS) and a negative regulator of the insulin signaling pathway. Thus GSK-3 inhibition increases the activity of GS and increases the activity of the insulin signaling pathway thus reducing blood glucose levels. Decreased blood glucose and increased serum insulin occurred in streptozotocin-induced T2DM male rats given ferulic acid (Roy et al. 2013). However, ferulic acid has yet to be tested in T2DM patients or in those at risk of T2DM.

Cinnamaldehyde is a derivative of CA and in streptozotocin-induced T2DM male Wistar rats was found to lower fasting plasma glucose levels and HbA1c (Babu et al. 2007). A decreased blood glucose observation has been made by Li et al. (2012) using cinnamaldehyde in db/db mice which may in part been due to the increased GLUT-4 mRNA expression observed by them in skeletal muscle of these animals. Furthermore, cinnamaldehyde administration to high fat diet-induced obese ICR mice resulted in lower plasma glucose levels (Huang et al. 2011). Abdelmageed et al. (2019) have found in a streptozotocin-induced T2DM rat model that cinnamaldehyde administration resulted in improved oral glucose and insulin tolerance as well as decreased fasting blood glucose, fasting blood insulin, HOMA-IR and increased HOMA-β index. The results were deemed attributable to increased activity of the insulin receptor substrate 1 (IRS) 1/phosphatidylinositol 3-kinase (PI3K) regulatory subunit 1/AKT serine/threonine kinase (AKT 2) pathway arising from increased expression of these proteins in the hepatic tissue of these animals. Kostrzewa et al. (2019) have indicated in an *in vitro* study that cinnamaldehyde had the potential to increase insulin sensitivity by inhibiting protein tyrosine phosphatase 1B thus potentially preventing T2DM or managing post-onset T2DM.

Cinnamaldehyde lowers diastolic blood pressure in insulin-resistant and insulin deficient male Wistar albino rats and systolic pressure in these insulin-deficient rats (El-Bassossy et al. 2011). Zhao et al. (2012), in a review paper, have indicated that ferulic acid-stimulated nitric oxide synthesis and angiotensin converting enzyme (ACE) inhibition that could lower systolic blood pressure in spontaneously hypertensive rats (SHR). Nitric oxide and inhibition of ACE act as vasodilators (Brown and Vaughan 1998; Chen et al. 2008), which allow blood pressure reduction. Ferulic appears better at lowering blood pressure than caffeic acid (Zhao et al. 2012). Interestingly, caffeic acid is a metabolite of chlorogenic acid (Zhao et al. 2012) suggesting the potential for chlorogenic acid administration in hypertension management. Agunloye and Oboh (2018) have indicated that chlorogenic acid and caffeic acid can inhibit plasma ACE in hypercholesterolemic rats. Unfortunately, Agunloye and Oboh (2018) did not measure blood pressure in these hypercholesterolemic rats. However, Bhandarkar et al. (2019) found that chlorogenic acid consumption decreased systolic pressure in male Wistar rats fed a high carbohydrate, high fat diet. Unfortunately, there appear to be no reports on the pre- or post-T2DM onset hypertension management by any of the CAs or their related compounds in humans.

Yoo et al. (2012) have found that an unspecified intraperitoneal dose of an unspecified CA (150 mg/kg body weight) in db/db T2DM mice decreased plasma cholesterol, LDL-c and triglycerides, and increased HDL-c. Wang et al. (2015) have found decreased

serum total cholesterol and triglycerides as the result of oral consumption of trans-CA in rats with alloxan-induced T2DM. These lipid levels were not changed in the human T2DM studies by Barre et al. (2012) and Pan et al. (2007) suggesting that the presence of CAs in the Barre et al. (2012) and Pan et al. (2007) studies was not sufficient to effect such changes. Cinnamate increases plasma HDLc, the HDLc:total cholesterol, and decreases total cholesterol and hepatic cholesterol (the lattermost via 3-hydroxyl-3-methyl-glutaryl CoA reductase inhibition) in high cholesterol- fed rats (Lee et al. 2003). Ferulic acid decreased plasma cholesterol and LDL cholesterol in db/db mice (Jung et al. 2007) and decreased serum cholesterol and triglycerides in streptozotocin-induced T2DM rats (Roy et al. 2013). Cinnamaldehyde increased serum HDLc in db/db mice (Li et al. 2012). Cinnamaldehyde when administered to streptozotocin-induced type 2 diabetic male Wistar rats was found to lower serum cholesterol and triglyceride levels and elevate plasma HDL-c concentrations (Babu et al. 2007). Similarly, cinnamaldehyde administration to high fat diet-induced obese ICR mice resulted in lower plasma fasting cholesterol and triglyceride levels (Huang et al. 2011). In a review paper that discussed the impacts of chlorogenic acid on lipid management, Meng et al. (2013) have noted that chlorogenic acid inhibits hepatic β-hydroxy-β-methylglutaryl-coenzyme A reductase in the livers of high fat diet-fed mice and in primary cultured rat hepatocytes thus helping to control plasma cholesterol levels. Agunloye and Oboh (2018) have indicated that chlorogenic acid decreased plasma cholesterol, LDL-c, and triglycerides while elevating HDLc in the hypercholesterolemic rats used in their study. Cho et al. (2010) have found reduced plasma cholesterol and triglyceride concentrations but no change in HDL-c concentrations due to each of chlorogenic acid and caffeic acid intake in high fat diet-induced obesity in mice. Chlorogenic acid administered to impaired glucose tolerance patients for 12 weeks resulted in lower plasma total cholesterol, LDL-c and triglycerides compared to baseline in the chlorogenic acid group (the placebo group showed no changes in any of these parameters) (Zuniga et al. 2018). Lee et al. (2004) have found that certain cinnamic amides could inhibit, *in vitro*, human acyl CoA:cholesterol acyl transferase 1- and 2- thus giving the potential for plasma cholesterol lowering.

Trans-CA, caffeic acid and ferulic acid lowered human platelet aggregation *in vitro* (Hubbard et al. 2003) as did chlorogenic acid (Amin et al. 2013). Lu et al. (2015) have noted that caffeic acid lowered mouse thrombus formation in vivo. Whether the significantly increased bleeding time, representative of lowered platelet reactivity, in the study by Barre et al. (2012) was due, in whole or in part, to any of the CAs present in the FLC is not clear. Pre-onset T2DM management of platelet hyperreactivity and hence shorter bleeding times has apparently not been studied in terms of CAs or their related compounds. Huang et al. (2007) have observed that cinnamaldehyde lowered platelet aggregation and thrombus formation in rats and mice.

Lee et al. (2004) have demonstrated antioxidant potential by three CA-related compounds (4-hydroxyCA (L-phenylalanine methyl ester) amide, 3, 4-dihydroxyhydroxyCA (L-aspartic acid dibenzyl ester) amide and 3, 4-dihydroxyhydroxy CA (L-alanine methyl ester) amide) against LDL oxidized with copper sulphate. However, Barre et al. (2012) did not find a decrease in LDL apoprotein B oxidation suggesting that any antioxidant effect would be CA or CA related compounds- or dose of each-specific i.e. not necessarily the CAs found in FLC. Various CAs have been reported to have a weak antioxidant impact relative to vitamin E using a linoleic acid model (Foti et al. 1996). Oxidized fatty acids are proposed to contribute to LDL's atherogenicity (Witztum and Steinberg 1991) and are thus worthy of in vivo assessment. Cinnamate decreased lipid peroxidation in high cholesterol diet- fed rats (Lee et al. 2003). However, no one appears to have published on the impact of CAs or their related compounds on lipid peroxidation pre- or post-T2DM onset in humans. Caffeic acid-induced oxidation reduction in the liver and erythrocytes of db/db mice (Jung et al. 2006) may have contributed to the finding of improved glucose management in db/db mice. In a review paper, Meng et al. (2013) have noted the serum antioxidant impact of chlorogenic acid in hyperlipidemic mice. Agunloye and Oboh (2018) indicated that chlorogenic acid had antioxidant properties in the hypercholesterolemic non-diabetic rats used in their study. Pari et al (2010) noted that chlorogenic acid decreased oxidation and inflammation in streptozotocin-induced T2DM male Wistar rats.

There appear to be no reports of CAs or their related compounds preventing or managing inflammation in pre- or post-onset human T2DM. Li et al. (2012) have observed a decrease in the pro-inflammatory cytokine TNF-α mRNA expression in adipose tissue of db/db mice fed cinnamaldehyde. Abdelmageed et al. (2019) have found, in a streptozotocin-induced T2DM rat model, that cinnamaldehyde administration resulted in reduced oxidation arising from increased hepatic and aortic superoxide dismutase

activity and increased glutathione. As well, decreased advanced glycation end products and expression of the receptor for these end-products was observed (Abdelmageed et al. 2019). The interaction of advanced glycation end products with their receptor has been linked to increased oxidation and inflammation (Schmidt et al. 2000). In that regard, Toma et al. (2017) have noted that caffeic acid reduced inflammation caused by glycated LDL in human endothelial cells (the advanced glycation end products receptor expression was also reduced by caffeic acid). Ferulic acid decreased lipid oxidation in pancreatic tissue and pro-inflammatory cytokines interleukin-1β (IL-1β and tissue growth factor-β1 (TGF-β1) expression in pancreatic beta cells in streptozotocin-induced T2DM rats (Roy et al. 2013). Furthermore, Khare et al. (2016) have observed, in male Swiss albino mice, a cinnamaldehyde-induced decrease in serum IL-1β, a pro-inflammatory cytokine that has been linked to poor glucose management. It has been suggested that IL-1β may have a role in T2DM onset (Zhao et al. 2014) and in glucose management post-T2DM onset (Cavelti-Weder et al. 2016). As such cinnamaldehyde may have a role to play in pre- and post-onset T2DM management.

A summary of the potential impacts of CAs and some of their associated compounds is found in Tables 1–7.

Conclusions

CAs (trans- and unidentified), an E isomer of CA-based thiazolidinedione and a metabolite of that isomer and a metabolite of that isomer, as well as p-methoxy CA, various cinnamic amides, chlorogenic acid, cinnamaldehyde, ferulic and caffeic acid are the compounds in this group of CAs and related compounds that have received the most attention. Unfortunately, relatively little work has been done with human pre- and post-onset T2DM with these compounds. Success in improving managing obesity, hyperglycemia, pro-thrombosis, and inflammation has been realized in one human post-onset T2DM trial and hyperglycemia in a second trial human post-onset T2DM trial both with FLC containing CAs, but those trials did not give pure CAs thus rendering impossible any conclusion about their impact. Trans-CA inhibits healthy human platelet aggregation *in vitro* and improves hyperglycemia and dyslipidemia in T2DM model rats. Chlorogenic acid has shown some promise in obesity, hyperglycemia and dyslipidemia in pre-T2DM onset humans with some suggestion of hyperglycemia management in post-T2DM onset. Much of the chlorogenic acid work in mammals has been done in non-pre- or post-T2DM model onset mice and rat models. In that regard, all but pro-thrombosis and inflammation can be managed by chlorogenic acid. Chlorogenic acid decreased inflammation in T2DM model rats and decreased *in vitro* platelet aggregation in healthy humans. Cinnamaldehyde, has not been investigated in humans but has been largely investigated in T2DM model rats and mice where all but pro-thrombosis management have shown success. Cinnamaldehyde decreased thrombus formation in non- pre- or post-T2DM rats and mice. Ferulic acid has not been investigated in humans except for success with *in vitro* platelet inhibition in healthy humans but has shown promise in all, but obesity, hypertension and pro-thrombosis in post-onset T2DM model rats and mice. Spontaneously hypertensive (non-pre- or post-onset T2DM) rats have angiotensin converting enzyme inhibition and thus potential to lower blood pressure in response to ferulic acid. Ferulic acid improves hyperglycemia, dyslipidemia, oxidation and inflammation in non-pre-or post-onset T2DM animals and decreases *in vitro* platelet aggregation in healthy humans. Caffeic acid improved all but oxidation and inflammation in non-pre- or post-onset T2DM rats or mice and only promise in post-T2DM onset mice model in terms of hyperglycemia and oxidation, but again there have been no human trials. With regard to all CAs and their associated compounds discussed herein, relatively little has been done with cell culture and *in vitro* work, but such studies are supportive of animal and/or human studies. Trans-CA has the potential to manage three, while each of chlorogenic acid, cinnamaldehyde, caffeic acid and ferulic acid have the potential to manage seven of the cluster of seven. Other compounds identified at best have potential to manage only one or two of the cluster of seven. There appear to be no reports on cis-CA. However, until many large pre- and post-T2DM onset human trials are undertaken, it is clear that there is insufficient information for the use of CAs and some of their related compounds in polypharmacy reduction in terms of safely and efficaciously combatting three or more members of the aforementioned seven features in both pre- and post-T2DM onset in the short and long term.

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Table 1
Impact of unspecified cinnamic acid or related compounds on the cluster of seven[1].

Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Human pre-onset T2DM							
Human post-onset T2DM							
Human non-pre- or post-onset T2DM							
Animal pre-T2DM							
Animal T2DM model		-lower fasting blood glucose levels in db/db T2DM mice (b) and in non-obese T2DM rats (c)		-decreased plasma cholesterol, LDLc, triglycerides, increased HDLc in db/db mice (b)			
Animal non-pre- or post-onset T2DM	-reduced extent of weight gain in high fat diet fed rats (a)			-cinnamate-increased plasma HDLc, HDLc:total cholesterol, decreased hepatic cholesterol in high cholesterol diet fed rats (f)		-cinnamate decreased lipid peroxidation in high cholesterol fed rats (f)	
Cell culture		-increased Glut-4 mRNA in L6 myotubes (d) -increased glucose-stimulated insulin secretion in isolated pancreatic islets (c) -increased glucose uptake in TNF-α induced insulin-resistant mouse hepatocytes (e)					
In vitro							

[1]Blank spaces under central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation refer to nothing found in the literature. (**a**) Mnafgui et al. 2015; (**b**) Yoo et al. 2012; (**c**) Cicero and Colletti 2016; (**d**) Lakshimi et al. 2009; (**e**) Huang et al. 2009; (f) Lee et al. 2003.

Table 2
Impact of trans-cinnamic acid and absence of cis-cinnamic acid impact on the cluster of seven[1].

Compound	Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Trans-cinnamic acid	Human pre-onset T2DM							
	Human post-onset T2DM							
	Human-non pre- or post-onset T2DM							
	Animal pre-T2DM							
	Animal T2DM model		-lowered serum glucose in the alloxan-induced T2DM rats, increased insulin secretion and activation of Glut-4 may be the explanation for such (a) improved glucose tolerance in streptozotocin-induced T2DM rats (b)		-decreased serum total cholesterol, triglycerides in alloxan-induced T2DM rats (a)			
	Animal non-pre- or post-onset T2DM							
	Cell culture		-increased adiponectin secretion by 3T3-L1 adipocytes, and in these cells, phosphorylation of AMPK-activated protein kinase via G-protein-coupled receptor signalling (c)					
	In vitro		-increased insulin secretion in isolated mice islets (b)			-lowered human platelet aggregation (d)		
Cis-cinnamic acid								

[1]Blank spaces under central obesity, hyperglycaemia, hypertension, dyslipidaemia, pro-thrombosis, oxidation and inflammation refer to nothing found in the literature. (**a**) Wang et al. 2015; (**b**) Hafizur et al. 2015; (**c**) Kopp et al. 2014; (**d**) Hubbard et al. 2003.

Table 3
Impact of a cinnamic acid-based drug, p-methoxycinnamic acid and cinnamic amides on the cluster of seven[1].

Compound	Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis
E isomer of a cinnamic acid-based thiazolidinedione, and a metabolite of that compound	Animal T2DM model[2]		-lowered blood glucose in ob/ob mouse model of T2DM (a cell culture study using HEK293 cells done by these authors as part of the same study suggested PPARγ activation as a mode of action for these two agents) (a)			
p-methoxycinnamic acid	Animal T2DM model[2]		-increased insulin secretion and glycolysis and decreased gluconeogenesis in streptozotocin-induced diabetic rats (b)			
Cinnamic amides (3 different amides)	*In vitro*[2]				-inhibition of human acyl CoA:cholesterol acyl transferase-1- and -2 thus giving potential for plasma cholesterol lowering (c)	-anti-oxidant potential in vitro against human LDL oxidation (c)

[1]Blank spaces under central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation refer to nothing found in the literature. [2]Other study types not included to save space. (**a**) Neogi et al. 2003; (**b**) Adisakwattana et al. 2005; (**c**) Lee et al. 2004.

Table 4
Impact of chlorogenic acid on the cluster of seven[1].

Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Human pre-onset T2DM	-mild waist circumference reduction in impaired glucose tolerance patients (a)	-decreased insulinogenic index and fasting plasma glucose in impaired glucose tolerance patients (a)		-lowered plasma total cholesterol, LDL-c and triglycerides compared to baseline in the chlorogenic acid group in impaired glucose tolerance patients (a)			
Human post-onset T2DM		-suggested mechanisms include inhibition of α-glucosidase, and elevated AMPK which increased GLUT-4 glucose capture in certain cells (b)					

Table 4
Continued . . .

Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Human non-pre- or post-onset T2DM	-increased fat oxidation during sleep (c)	-lower glucose and insulin concentrations at 15 min post- glucose consumption in a glucose tolerance test in 15 overweight men (d)					
Animal pre-T2DM	-reduced energy intake, waist circumference and visceral adiposity in rats fed a high carbohydrate, high fat diet (e)						-reduced inflammation in rats fed a high carbohydrate, high fat diet (e)
Animal T2DM model		-inhibited hepatic glucose-6-phosphatase in db/db mice (f)				decreased oxidation in streptozotocin-induced T2DM male Wistar rats (g)	
Animal non-pre- or post- onset T2DM	-found reduced body weight, visceral fat mass and plasma leptin in high fat diet-induced obesity in mice (h) -suppress weight gain in mice (b)	-decreased plasma insulin in high-fat induced obese mice (h)	-inhibit plasma angiotensin converting enzyme in hypercholesterolemic rats (i) -decreased systolic pressure in male Wistar rats fed a high carbohydrate, high fat diet (e)	-decreased plasma cholesterol, LDLc, triglycerides, elevated HDLc in hypercholesterolemic rats (i) -reduced plasma cholesterol and triglyceride concentrations but no change in HDLc concentrations in high fat diet-induced obesity in mice (h) -inhibited hepatic hydroxymethyl glutaryl coenzyme A reductase in the livers of high fat diet-fed mice - thus potential to lower plasma cholesterol (b)		-antioxidant properties in hypercholesterolemic rats (i) -serum antioxidant impact in hyperlipidemic mice (b)	
Cell culture		-cultured L6 myotubes (AMPK mediated GLUT-4 glucose capture) (j)		-inhibited hydroxymethyl glutaryl coenzyme A reductase in primary cultured rat hepatocytes-thus potential to lower plasma cholesterol (b)			

Table 4
Continued . . .

Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
In vitro		-weak inhibitor of human salivary α-amylase relative to Acarbose (k) -hepatic glucose-6 -phosphatase inhibitor (rat) (l) -inhibits porcine pancreatic α-amylase (m) -inhibits porcine pancreatic α-amylase and α-glucosidase (from Saccharomyces cerevisiae) (n)			-lowered human platelet aggregation (o)		

[1]Blank spaces under central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation refer to nothing found in the literature. (**a**) Zuniga et al. 2018; (**b**) Meng et al. 2013; (**c**) Park et al. 2017; (**d**) Van Dijk et al. 2009; (**e**) Bhandarkar et al. 2019; (**f**) Ong et al. 2013; (**g**) Pari et al 2010; (**h**) Cho et al. 2010; (**i**) Agunloye and Oboh 2018; (**j**) Ong et al. 2012; (**k**) Nyambe- Silavwe et al. 2018; (**l**) Madsen and Westergaard 2001; (**m**) Funke and Melzig 2006; (**n**) Oboh et al. 2015; (**o**) Amin et al 2013.

Table 5
Impact of cinnmaldehyde on the cluster of seven[1].

Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Human pre-T2DM							
Human T2DM							
Human non-pre- or post-onset T2DM							
Animal pre-T2DM							

Table 5
Continued . . .

Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Animal T2DM model	-lowered body weight in db/db mice (a T2DM model) (a) but it is not clear if that represented fat mass reduction	-better oral glucose and insulin tolerance tests, decreased fasting blood glucose, fasting blood insulin, HOMA-IR and increased HOMA-% - all attributable to increased IRS1/PI3K regulatory subunit AKT 2 pathway activity in hepatic tissue of streptozotocin-induced T2DM rat model (b) -lower blood glucose in db/db mice - may in part have been due to increased GLUT-4 mRNA expression in skeletal muscle (a) -lower plasma glucose and HbA1c in streptozotocin-induced T2DM male Wistar rats (c)	-lowered diastolic blood pressure in insulin-resistant and insulin deficient male Wistar albino rats and systolic pressure in these rats that are insulin deficient (d)	-increased serum HDLc in db/db mice (a) -lowered serum cholesterol and triglyceride levels, elevated plasma HDL-c concentrations in streptozotocin-induced type 2 diabetic male Wistar rats (c)		-reduced oxidation arising from increased hepatic and aortic superoxide dismutase activity and increased glutathione in a streptozoto-cin-induced T2DM rat model (b)	-decreased advanced glycation end products and expression of the receptor for these endproducts (b) -the interaction of advanced glycation end products with their receptor has been linked to increased oxidation and inflammation (e) -decreased pro-inflammatory cytokine TNF-α mRNA expression in adipose tissue of db/db mice (a)
Animal non-pre- or post- onset T2DM	-slower weight gains in high fat diet-induced obese ICR mice; there was no specific indication of fat mass gain reduction though reduced lipid accumulation in 3T3 L1 differentiated adipocytes (f) -decreased weight in high fat fed Swiss male albino mice partly due to decreased serum leptin:ghrelin ratio (h) -this decreased ratio reduces weight gain (i)	-lowered plasma fasting glucose levels in high fat diet induced obese ICR mice (f)		-lowered plasma fasting cholesterol and triglyceride levels in high fat diet-induced obese ICR mice (f)	-decreased thrombus formation in rats and mice (g)		-decreased serum IL-1β, a pro-inflammatory cytokine, in Swiss albino mice (h)

Table 5
Continued . . .

Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Cell culture	-reduced lipid accumulation in mature adipocytes arising from 3T3- L1 pre-adipocytes- due in part to a phenotypic shift toward lipolysis (h)						
In vitro		-potential to increase insulin sensitivity by inhibiting protein tyrosine phosphatase 1B thus potentially preventing T2DM or managing post -onset T2DM (j)			-lowered platelet aggregation in rats and mice (g)		

[1]Blank spaces under central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation refer to nothing found in the literature. (**a**) Li et al. 2012; (**b**) Abdelmageed et al. 2019; (**c**) Babu et al. 2007; (**d**) El-Bassossy et al. 2011; (**e**) Schmidt et al., 2000; (**f**) Huang et al. 2011; (**g**) Huang et al. 2007; (**h**) Khare et al. 2016; (**i**) Crujeiras et al. 2014; (**j**) Kostrzewa et al. 2019.

Table 6
Impact of ferulic acid on the cluster of seven[1].

Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Human pre-T2DM							
Human T2DM							
Human non-pre- or post-onset T2DM							
Animal pre-T2DM							

Table 6
Continued . . .

Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Animal T2DM model		-decreased blood glucose in db/db mice associated with increased plasma insulin and hepatic glycogen synthesis (c) -decreased blood glucose and increased serum insulin in streptozotocin-induced T2DM male rats (d)		-decreased plasma cholesterol and LDL cholesterol in db/db mice (c) -decreased serum cholesterol and triglycerides in streptozotocin-induced T2DM rats (d)		-decreased lipid oxidation in pancreatic tissue in streptozotocin-induced T2DM rats (d)	-decreased IL-1β and TGF-α in pancreatic beta cells in streptozotocin-induced T2DM rats (d)
Animal non- pre- or post- onset T2DM	-suppressed visceral fat accumulation and obesity (a) and hepatic fat (b) in high fat diet-induced obese mice		-stimulated nitric oxide synthesis and angiotensin converting enzyme inhibition could lower systolic blood pressure in spontaneously hypertensive rats (f)				
Cell culture							
In vitro		-potential glycogen synthase kinase-3 inhibition (molecular docking studies) (e) -baker's yeast α-glucosidase inhibition (c)			-decreased in vitro human platelet aggregation (g)		

[1]Blank spaces under central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation refer to nothing found in the literature. (**a**) de Melo et al 2017; (**b**) Wang et al. 2018; (**c**) Jung et al. 2007; (**d**) Roy et al. 2013; (**e**) Devi et al. 2018; (**f**) Zhao et al. 2012; (**g**) Hubbard et al. 2003.

Table 7
Impact of caffeic acid on the cluster of seven[1].

Nature of Study	Obesity	Hyperglycemia	Hypertension	Dyslipidemia	Pro-thrombosis	Oxidation	Inflammation
Human pre-T2DM							
Human T2DM							
Human non-pre- or post-onset T2DM							
Animal pre-T2DM							
Animal T2DM model		-decreased fasting blood glucose in db/db mice in part due to increased adipose Glut-4 expression and decreased hepatic glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (b)				-induced reduction in oxidation in liver and erythrocytes of db/db mice (i)	
Animal non-pre- or post- onset T2DM	-reduced body weight, visceral fat mass and plasma leptin due in high fat diet-induced obesity in mice (a)	-decreased plasma insulin in high-fat diet induced obese mice (a)	-ferulic better at lowering systolic pressure than caffeic in spontaneously hypertensive rats (e) -inhibits plasma angiotensin converting enzyme in hypercholesterolemic rats (f)	-reduced plasma cholesterol and triglyceride concentrations but no change in HDL-c in high fat diet-induced obese mice (a)	-lowered mouse thrombus formation in vivo (g)		
Cell culture		-improved glucose uptake in TNF-α induced insulin-resistant mouse hepatocytes (c)					-reduced in human endothelial cells (j)
In vitro		-inhibits porcine pancreatic α-amylase and α-glucosidase (Sacch-aromyces cere-visiae) (d)			-lowered human platelet aggregation (h)		

[1]Blank spaces under central obesity, hyperglycemia, hypertension, dyslipidemia, pro-thrombosis, oxidation and inflammation refer to nothing found in the literature. (**a**) Cho et al. 2010; (**b**) Jung et al. 2006; (**c**) Huang et al. 2009; (**d**) Oboh et al. 2015; (**e**) Zhao et al. 2012; (**f**) Agunloye and Oboh 2018; (**g**) Lu et al. 2015; (**h**) Hubbard et al. 2003; (**i**) Jung et al. 2006; (**j**) Toma et al. 2017.

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