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Response to Reviewers: Editor's comments:

The revised version fulfill most of the reviewer requests, so I'm willing to accept your paper. However before the final acceptance I ask you to
1) Add four highligts (one line each)
2) Add a graphical abstract

Authors' response:

Thank you for the response to the re-submission of our manuscript. We have now included four highlights and a graphical abstract as requested.

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FAO:

Profesor Vincenzo Fogliano
Editor-in-Chief
Journal of Functional Foods

29h April 2018

Dear Professor Fogliano,

Thank you for the response to the resubmission of our manuscript entitled 'Coffee, type 2 diabetes and pancreatic islet function - a mini-review' (Ms. Ref. No.: JFF-D-18-00148R1). We have now included highlights and a graphical abstract as requested. I hope this satisfies all the requirements and look forward to hearing from you in the near future.

Yours sincerely,

Astrid Hauge Evans, PhD

Senior Lecturer in Nutrition and Health
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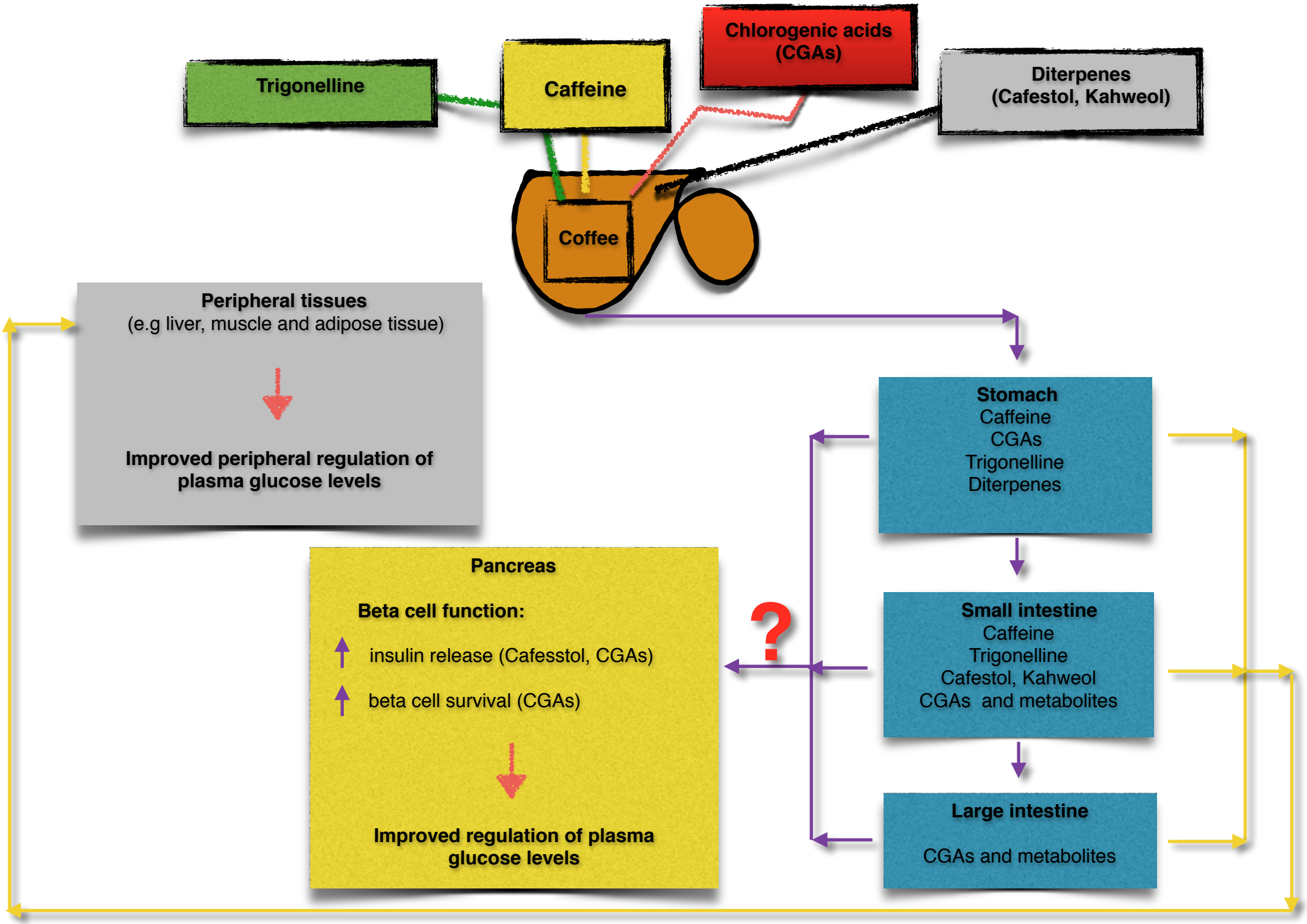
Highlights

- Coffee consumption is linked to reduced risk of type 2 diabetes
- Bioactive coffee components enhance peripheral regulation of blood glucose levels
- Review evaluates effect of coffee derivatives on pancreatic beta cell function
- Selected coffee compounds stimulate insulin release; effect on beta cell survival unclear

Graphical abstract



Coffee, type 2 diabetes and pancreatic islet function - a mini-review

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Abstract

Caffeinated and decaffeinated coffee consumption has increasingly been linked to reduced risks of type 2 diabetes. The condition is characterised by insulin resistance and pancreatic beta cell loss and dysfunction, leading to hyperglycaemia. Recent research has indicated that coffee components such as chlorogenic acid derivatives and cafestol positively modify the regulation of blood glucose levels in peripheral tissues. Taking into consideration bioavailability of coffee bioactives, this mini-review evaluates the pros and cons of individual components and their combinations and highlights some of their significant effects on insulin secretion. Although the loss and/or dysfunction of beta cells is a key element in type 2 diabetes, little is known about the impact of coffee components on the regulation of beta cell mass, including survival under conditions of hyperglycaemia, lipotoxicity and inflammation. Further investigations are warranted in particular with regards to use of physiologically relevant concentrations and conjugated forms of the bioactive components.

Key words

Coffee, type 2 diabetes, islet, beta cell function, chlorogenic acids

Abbreviations

CGA:	Chlorogenic acid
GLP1:	Glucagon-like-peptide 1
HOMA:	Homeostatic model assessment
IR:	Insulin resistance
STZ:	Streptozotocin
T2D:	Type 2 Diabetes

1. Introduction

The increasing incidence of type 2 diabetes (T2D) constitutes a significant health issue with the condition being one of the top 10 causes of death worldwide (World Health Organisation (WHO), 2017). It is therefore imperative to find solutions to the management and prevention of diabetes, and potential beneficial effects of natural compounds have become a point of focus in medical research. However, despite reports of their potential preventive role in diabetes, natural compounds of interest are not necessarily easily accessible for the general consumer as part of a regular diet (such as for example a range of plant components traditionally used in Chinese medicine, e.g. extract of White Kwao Krua (*Pueraria Lobata,* (Xiong, Sun, Gan, Yang, & Xu, 2006) or puerarin from *Rhizoma Coptidis* (E. K. Kim et al., 2007). It is therefore relevant to assess whether habitually consumed compounds found in regular food and drink may indeed provide readily available and novel benefits.

Coffee is among one of the most frequently consumed drinks worldwide and regular, long-term consumption of both caffeinated and de-caffeinated coffee has been shown to reduce the risk of T2D (Bhupathiraju et al., 2013; Ding, Bhupathiraju, Satija, van Dam, & Hu, 2014; Jiang, Zhang, & Jiang, 2014; Odegaard et al., 2008; van Dam & Hu, 2005). In addition to caffeine, coffee contains a variety of other compounds. One such group is chlorogenic acids (CGAs), a family of polyphenolic compounds which in other disease settings exhibits protective properties and in T2D has been suggested to affect a number of factors relevant for the regulation of blood glucose levels, including intestinal glucose uptake, hepatic glucose output and oxidative stress in the liver (Santos & Lima, 2016).

T2D is a complex disease which is characterised by insulin resistance in the insulin target tissues and insulin secretory dysfunction with significant loss of functional beta cells in the pancreas leading to hyperglycaemia. So far, studies investigating the association between the potential effects of coffee derivatives and T2D have focused on roles in peripheral tissues, such as improving insulin sensitivity and to a lesser extent a central effect on insulin secretion. The aim of this narrative review is to evaluate current knowledge and the most updated evidence on the effect of coffee compounds and in particular CGAs on T2D risk with specific focus on pancreatic islet function and consequent impact on insulin release and beta cell survival.

2. Bioavailability of major coffee components and their metabolites

Coffee is a complex mixture of chemical compounds (table 1) and its composition varies according to the species of coffee bean and the roasting and brewing processes involved. Caffeine, a methylxanthine, is the most well-known component, but the beverage also contains a range of other components, some of which are minerals (e.g. magnesium and potassium), diterpenes such as cafestol and kahweol, the plant alkaloid trigonelline as well

as more than a thousand phenolic compounds. Of these, chlorogenic acids (CGAs) are the most prevailing (Ludwig, Paz de Pena, Concepcion, & Alan, 2013; Moon & Shibamoto, 2009).

Caffeine intake per serving ranges between 51-322 mg (Crozier, Stalmach, Lean, & Crozier, 2012). The compound is readily absorbed in the stomach and small intestine and is distributed throughout the body via the circulation but is also further metabolized in the liver to a range of metabolic derivatives (Arnaud, 2011). Depending on variety, roasting and coffee making procedure a coffee serving contains 40-110 mg trigonelline but in contrast to caffeine, there is limited production of secondary metabolites from the compound although it is also readily detected in plasma samples in the micromolar range (Lang et al., 2013). Diterpenes are found as fatty acyl esters in coffee and are known to increase cholesterol plasma levels. Their content is reduced in coffee by preparation methods involving paper or fabric ('sock') filtration. Thus Naidoo et al. (2011) found that unfiltered coffee such as boiled Scandinavian coffee or Turkish/Greek coffee contained 0.4-9.68 mg/cup of cafestol and 0.08-11.68 mg/cup kahweol, respectively, whereas filtered coffee contained much less (e.g. Singapore coffee: 0.02-0.23 mg/cup cafestol and 0.01-0.06 mg/cup kahweol, respectively, Naidoo et al., 2011).

Caffeic acid, and its derivatives, the CGAs, are the most common phenolic compounds in coffee and Richelle et al. (2001) reported that a single serving of the beverage contains between 15 and 325 mg/cup depending on type of coffee, roasting and brewing methods, although there is some variation between different studies regarding these values (e.g. Crozier et al., 2012; Mills, Oruna-Concha, Mottram, Gibson, & Spencer, 2013; Stalmach et al., 2009). CGAs are esters of caffeic or ferulic acid and quinic acid, and a wide variety of isomers exist in the CGA family, of which 5-caffeoyl-quinic acid (5-CQA) is the most abundant in coffee reviewed in Cano-Marquina, Tarin, & Cano, 2013).

In order to exhibit any physiological effect on metabolic regulation including islet function, the bioavailability of the CGAs is of paramount importance. A number of studies has measured physiologically relevant concentrations of CGAs and particularly their metabolites in the circulation in both rodents and man, but also highlighted the fact that there are high levels of variation between individuals, and that different isomers are absorbed and metabolized to varying degree (Farah, Monteiro, Donangelo, & Lafay, 2008; Gonthier, Verny, Besson, Remesy, & Scalbert, 2003; Mills et al., 2013; Monteiro, Farah, Perrone, Trugo, & Donangelo, 2007; Stalmach, Williamson, & Crozier, 2014).

In the gastrointestinal tract a small proportion of ingested CGAs is hydrolysed to caffeic (and ferulic) acid by enzymatic activity and absorbed in the small intestine via monocarboxylic acid transporters or other means of carrier-mediated transport. In addition passive diffusion has also been proposed as a potential mechanism (El-Seedi et al., 2012; Zhao & Moghadasian, 2008). The compounds are subsequently conjugated and likely constitute the

initial wave of increased plasma concentrations of CGAs following a CGA-rich intake (Stalmach et al., 2014). Absorption and metabolism of phenolic acids also take place in the large intestine, where the microbiota plays an important role in further catabolizing and modifying the precursor compounds (Anhê et al., 2013; Olthof, Hollman, Buijsman, van Amelsvoort, & Katan, 2003). Some *in vitro* and *in vivo* studies have shown the potential prebiotic effects of phenolic acids to increase the population of healthy beneficial bacteria such as bifidobacteria whilst decreasing adverse populations (Chacar et al., 2018; Duncan et al., 2016; Xie et al., 2017). Thus the resulting metabolic end products from the large intestine are likely to be quantitatively more important contributors to the circulating levels of physiologically relevant metabolites than those from the small intestine and contribute to a later peak of CGAs in the blood (Gonthier et al., 2003; Renouf et al., 2010; Stalmach et al., 2014).

3. Impact of bioactive coffee components on insulin resistance and other non-pancreatic aspects of blood glucose control

The key issue in diabetes, whether type 1 or type 2, is the derangement of blood glucose homeostasis with subsequent hyperglycaemia. In T2D this is caused by a combination of insulin resistance in the insulin target tissues and insulin secretory dysfunction in pancreatic beta cells. De-regulated blood glucose levels have acute health consequences, but also lead to long-term complications such as neuropathy, nephropathy, retinopathy and increased risk of cardiovascular disease. Blood glucose control is therefore sought therapeutically via improvement of insulin sensitivity in muscle and adipose tissues with concomitant changes in glucose uptake into the cells and via enhancement and preservation of insulin secretion from the pancreatic beta cells. However, other means of regulating glucose homeostasis are also of interest, for example at the level of glucose uptake from the intestine and production of glucose in the liver. Beta cell function is the main focus of this review, and the role of coffee components in peripheral tissues has been reviewed elsewhere (see for example Adisakwattana, 2017; Tajik, Tajik, Mack, & Enck, 2017), therefore only a brief summary will be presented to provide context (see figure 1).

A number of human studies (e.g. Agardh et al., 2004; K. Kim, Kim, & Park, 2016; Lecoultre et al., 2014; Pham et al., 2015; Sarria et al., 2016) suggest that coffee consumption leads to a reduction in insulin resistance thus supporting the notion that coffee components can directly modify insulin sensitivity in peripheral tissues although this does not specify the specific points of potential action (please refer to figure 1). The findings in humans are consistent with animal studies such as for example that of Shokouh et al. (2017), who very recently showed that a twelve week diet intervention with a combination of caffeic acid, trigonelline and cafestol led to improved insulin sensitivity in a rat model of the metabolic syndrome. Ma, Gao, & Liu (2015) similarly reported of reduced insulin resistance and attenuated inflammation of liver and white tissue in C57BL/6 mice fed a high fat diet for 15 weeks following administration of CGAs twice weekly. Intraperitoneal administration of CGA

in $Lepr_{db/db}$ mice (an animal model of type 2 diabetes) was specifically shown to reduce hepatic glucose-6-phosphatase expression and activity and thus gluconeogenesis in liver in addition to inhibiting fatty acid synthesis and improving muscle glucose uptake (Ong, Hsu, & Tan, 2013), thus providing some information on potential underlying peripheral mechanisms of action.

Some *in vitro* studies supported the effect of CGAs and derivatives on glucose uptake in muscle; this was, however, dependent on type of derivative and with relatively high concentrations providing moderate effects (Azay-Milhau et al., 2013; Tousch et al., 2008). More significant changes regarding glucose uptake were observed in a liver cell line (Huang, Shen, & Wu, 2009). In addition Mellbye et al. reported of clear beneficial effects on glucose uptake in a muscle cells by another coffee component, cafestol (Mellbye, Jeppesen, Hermansen, & Gregersen, 2015).

The effect of caffeine on insulin sensitivity depends on type of administration, where acute intake has in fact been shown to induce insulin resistance in rodents and man (Dewar & Heuberger, 2017; Greer, Hudson, Ross, & Graham, 2001; Sacramento et al., 2015; Shi, Xue, Liang, Zhao, & Zhang, 2016), whereas chronic intake prevented diet-induced insulin resistance in rats (Conde et al., 2012), possibly due to the development of caffeine tolerance.

Other reported T2D-related outcomes with coffee compounds include an inhibitory effect of CGAs on glucose uptake in the intestine and stimulation of glucagon-like-peptide 1 (GLP1) secretion from gastrointestinal cells, which in turn can modify gastric emptying and stimulate insulin secretion (Fujii, Osaki, Hase, & Shimotoyodome, 2015; Johnston, Clifford, & Morgan, 2003). However, contradictory results exist regarding the impact on GLP1 and thus indirectly on insulin release (Tunnicliffe, Eller, Reimer, Hittel, & Shearer, 2011).

4. Coffee and pancreatic islet function in type 2 diabetes

The hormone insulin is produced by beta cells in the pancreatic islets of Langerhans. Hyperinsulinemia is often seen as a response to insulin resistance and is a compensatory mechanism where the pancreatic beta cells produce more insulin to counteract the reduced insulin sensitivity of the peripheral tissues. In addition to this increased demand for hormone production, the cells are also persistently exposed to a local environment of inflammation and (gluco)lipotoxicity during the development of T2D and with time this has detrimental effects on beta cell function and mass (Chang-Chen, Mullur, & Bernal-Mizrachi, 2008a). Protection and/or improvement of beta cell survival under these conditions is therefore a key area of research in order to postpone or indeed prevent beta cell loss and subsequent reduction in secretory capacity.

4.1 Human studies on beta cell function

There is limited evidence for the role of coffee derivatives on beta cell function and insulin secretion from human studies. Whereas a range of findings suggest that coffee consumption reduces the relative risk of insulin resistance (as indirectly measured by the HOMA-IR index) in healthy (Rebello et al., 2011), non-diabetic overweight (Wedick et al., 2011) and obese individuals (Pham et al., 2015), these studies did not observe any changes in beta cell function when measured indirectly by the HOMA-beta index assessment. However, the population studies by Rebello et al. (2011) and Pham et al. (2015) did not distinguish between caffeinated and decaffeinated coffee consumption, in contrast to the much smaller, randomized parallel-arm intervention study by Wedick et al. (2011). It is therefore possible that potential separate effects of caffeine and non-caffeine components of coffee went unnoticed in these studies.

This notion is supported by a cross-sectional study (Loopstra-Masters, Haffner, Lorenzo, Wagenknecht, & Hanley, 2011) involving 954 multi-ethic non-diabetic individuals from the Insulin Resistance Atherosclerosis Study (IRAS). Results from this study showed that caffeinated coffee intake was associated with an increase in peripheral insulin sensitivity with no effect on the acute insulin release, whereas decaffeinated coffee positively affected beta cell function, as measured by multiple regression analyses of the acute insulin response and ratios of proinsulin and C-peptides.

In addition, the health status of study participants is likely to be important in this context. Thus Agardh et al. (2004) found that coffee consumption (>5 cups/d) reduced the relative risk of type 2 diabetes and impaired glucose tolerance in a Swedish population of middle-aged, healthy individuals as has been reported elsewhere in other healthy population groups. However, they also showed that increased coffee intake was inversely associated with reduced beta cell function in addition to any effect on insulin sensitivity specifically in individuals diagnosed with type 2 diabetes. Thus men diagnosed with T2D consuming >5 cups per day showed 60 and 70% reduction in the relative risk of insulin resistance and low beta cell function, respectively vs men consuming 2 cups or less, whereas in women the relative risks were 70 and 50%, respectively. This suggests firstly, that coffee components may be of particular importance not only for risk reduction, but also for management of the condition and secondly, that under those circumstances, beta cell function was impacted by coffee. Studies like this cannot, however, unambiguously clarify whether such effects are indirectly caused by changes in peripheral parameters or by direct effects of coffee components on pancreatic islet function. For that purpose *in vitro* and *ex vivo* experiments with whole pancreata, isolated islets and/or pancreatic beta cell lines are of particular value as experimental research models.

4.2 *In vitro* research models

The insulin-producing beta cells are located in small, three-dimensional clusters of cells, the islets of Langerhans, and in a human pancreas there are approximately 1 million islets distributed in the exocrine tissue of the pancreas, in the size range of 50-500 µm (Pipeleers,

Kiekens, & In't Veld, 1992). The islets contain other types of cells in addition to beta cells, of which glucagon-secreting alpha cells and somatostatin-producing delta cells are the most important. These cells interact to modify and regulate the overall hormonal output from the islet (Hauge-Evans et al., 2009; Van Schravendijk et al., 1985), and to fully understand the role of coffee derivatives in the regulation of insulin secretion and beta cell function in general, it is therefore important firstly to assess the impact of these compounds on other islet cell types and secondly to employ research models where non-beta cell input has been eliminated or minimised.

Pancreatic beta cell lines constitute initial useful models for investigating beta cell function, particularly if the cells are configured as three-dimensional 'pseudoislets' (Hauge-Evans, Squires, Persaud, & Jones, 1999), which facilitate a higher degree of cell-cell contact similar to that of the primary micro-organs. We have thus previously shown that the three-dimensional structure of pseudoislets from the pancreatic MIN6 beta cell line conveys superior functionality compared to MIN6 cells configured as two-dimensional monolayers, whilst at the same time enabling specific studies on beta cell function only (Hauge-Evans et al., 1999). Beta cell lines do, however, have limitations compared to primary islet tissue with regards to issues such as levels of insulin content and secretory response (Persaud, Hauge-Evans, & Jones, 2014), and it is therefore paramount to support any initial findings with studies involving primary islets. Isolated islets furthermore provide a research model in which the impact of target compounds on insulin secretion and overall beta cell function can be investigated under conditions where factors from both peripheral and central tissues are excluded and therefore do not mask any direct action on the beta cells. For this specific purpose they are therefore more informative than *in vivo* studies, although findings from *in vitro* studies need to be followed up by *in vivo* studies to confirm their physiological relevance. In addition to cell line and isolated islet studies, *ex vivo* experiments with perfusion of whole, *in situ* isolated pancreata are informative for assessment of islet hormone secretion, incorporating local factors within the pancreatic exocrine tissue but excluding effects of other organs. However some interaction with the duodenum cannot be excluded (Scratcherd & Case, 1973).

When considering the importance of coffee derivatives on beta cell function, a potential impact on beta cell viability have to date often been overlooked even if the maintenance of adequate beta cell mass is essential for maintaining sufficient release of insulin. Thus, both assessments on insulin secretion and overall regulation of beta cell mass including beta cell survival and proliferation is required to evaluate the impact of coffee derivatives, in particular in the context of the development of T2D, where the islet is exposed to a range of cellular factors negatively impacting cell survival.

4.3 Coffee compounds and insulin secretion

Caffeine has been known to stimulate glucose-induced insulin secretion for a long time. The effect is thought to be mediated both via activation of ryanodine receptors affecting

intracellular Ca^{2+} concentrations and via inhibition of antagonistic effects of cAMP-phosphodiesterases on hormone release (Bruton et al., 2003; Sams & Montague, 1972).

In contrast, there are a limited number of studies directly investigating the role of non-caffeine coffee derivatives with regard to insulin secretion. Mellbye et al. (Mellbye et al., 2015) performed an *in vitro* study with the rat insulinoma beta cell line INS1E, where they investigated acute insulin release in response to selected compounds representative of the main components in coffee, that is, cafestol, caffeic acid, chlorogenic acid, trigonelline, secoisolariciresinol and oxokahweol. Only cafestol and caffeic acid modestly, but significantly, stimulated glucose-induced insulin release and also improved release following prolonged exposure to the two coffee components at metabolically relevant concentrations (10^{-10}-10^{-8}mol/l). This investigation was followed up by an *in vivo* study in the KKay animal model of type 2 diabetes (Tomino, 2012), where animals received a low or high cafestol-containing diet for ten weeks, leading to reduced fasting glucose levels, increased insulin sensitivity and significantly improved insulin secretion from isolated islets (Mellbye et al., 2017). Unfortunately no oral glucose tolerance test was performed to give specific information on both glucose levels and insulin release following a glucose challenge. Kafestol content in coffee is reduced by paper filtration, and it is questionable whether the concentrations used in the rodent model (when translated to human parameters) compare to circulatory levels following consumption in the majority of the general population and therefore can constitute a significant explanatory factor for the observed beneficial effects of coffee in population studies. Nonetheless, the study provided important evidence of a potential therapeutic role of the coffee derivative although at pharmacologically rather than physiologically relevant concentrations.

The beneficial, but moderate effect of caffeic acid on acute insulin secretion reported by (Mellbye et al., 2015) was consistent with the findings of Bhattachaya et al. (2014), who also showed that chronic exposure to the phenolic acid further enhanced the secretory response from INS1E beta cells. This effect was maintained following chronic treatment with high glucose concentrations, suggesting a protective effect of the compound on beta cell survival when exposed to stressful conditions typical of type 2 diabetes. Unfortunately these findings were not confirmed in primary islets. Azay-Milhau et al. (2013) did not find any stimulatory effect of caffeic acid on insulin secretion, probably due to the non-stimulatory glucose concentrations used in these experiments. However, an extract of chicoric acid, another hydroxycinnamic acid (2,3-dicaffeoltartaric acid), did stimulate release at these glucose concentrations, confirming previous results on chicoric acid from this research group (Tousch et al., 2008).

There is thus conflicting evidence for an effect of caffeic acid on insulin secretion and also whether the phenolic acids tested modify secretion in a glucose-dependent or independent manner. In addition, the importance of conjugates was not evaluated, even though Stalmach et al. (2009; 2014) suggest that caffeic acid-3'-O-sulphate and ferulic-4'-O-sulfate

are the main metabolites in the circulation from the small intestine (in the range of 65-126 nmol/l). These studies and similarly findings by Renouf et al. (2010) also showed that dihydrocaffeic and dihydroferulic acids and their sulphate-conjugated derivatives were much more abundant than the parent compounds in plasma from human subjects following coffee intake (1-500 nmol/l), highlighting the importance of microbiota-derived catabolites. Ludwig et al. (2013) similarly found that catabolism of coffee CGAs by microbiota from human faecal samples *in vitro* only transiently led to the production of caffeic and ferulic acid, whereas the main catabolic end products were dihydrocaffeic, dihydroferulic and 3-(3'-hydroxyphenyl)propionic acid, making up approximately 80% of the total metabolites produced.

Of interest here are also the studies by Adisakwattana, Moonsan, & Yibchok-Anun (2008), who investigated the role of cinnamic acid and hydroxy- or methoxy-cinnamic acid derivatives as well as ferulic and isoferulic acid in the regulation of insulin secretion. It was clear from their studies that the position of the hydroxy- and methoxy- groups influenced the secretagogue potential of the different compounds with m-hydroxycinnamic, p-methoxycinnamic and ferulic acid stimulating insulin release from INS1E cells and perifused pancreas at low glucose concentrations whereas other derivatives were less effective. Unfortunately the concentrations used were predominantly high (100 µmol/l) compared to physiologically relevant concentrations, although the same group in a later study reported that 10 µmol/l p-methoxycinnamic acid further enhanced glucose-induced insulin release from the perfused pancreas (Yibchok-anun, Adisakwattana, Moonsan, & Hsu, 2008). More recently, the parent compound, cinnamic acid, improved glucose tolerance *in vivo* and increased insulin secretion *in vitro* from isolated islets, however, again at high concentrations (50, 100 and 200 µmol/l, Hafizur et al., 2015). There is therefore a current need for future studies which investigates the role of coffee-derived phenolic acids, where physiologically relevant metabolites, rather than parent compounds, are investigated at concentrations which are comparable with circulating levels in the body following coffee consumption.

4.4 Coffee compounds and beta cell survival

As mentioned, development of type 2 diabetes is associated with the deterioration of beta cell function and/or mass and it is therefore relevant not only to investigate how coffee-derived compounds affect insulin secretion directly, but also whether they may convey potential protective properties to the pancreatic islet, thus delaying or minimising the detrimental effects of cellular stresses such as gluco- and lipotoxicity, oxidative stress and inflammation associated with the condition (Chang-Chen, Mullur, & Bernal-Mizrachi, 2008b; Cnop et al., 2005; Marchetti, Dotta, Lauro, & Purrello, 2008; Poitout & Robertson, 2008). Whereas inflammation for example may be reduced systemically via action of coffee compounds on other tissues, the key question here is whether there is a direct, protective effect on the pancreatic beta cell. Beta cell mass is regulated by cell death, but also by cell

replication and hypertrophy (Bonner-Weir et al., 2010). The role of coffee derivatives in all these cellular processes and the underlying cellular mechanisms are therefore of interest.

One coffee component, trigonelline, a plant alkaloid, reportedly exhibit antioxidant properties in pancreatic tissue (Zhou, Zhou, & Zeng, 2013). CGAs also harbour strong antioxidant activities *in vitro* although the relative importance *in vivo* compared to other dietary antioxidants have been questioned in recent years (Ludwig, Clifford, Lean, Ashihara, & Crozier, 2014). It is thus suggested that the cellular mode of action for CGAs and derivatives may involve direct modulation of intracellular pathways leading for example to changes in gene expression (Miene, Weise, & Glei, 2011). Coffee components may therefore not only benefit beta cells through their antioxidant properties but also via alternative pathways.

Streptozotocin (STZ)-induced diabetes is often used as an animal model for type 1 rather than type 2 diabetes, since injection of high doses STZ (>50mg/kg) leads to destruction of beta cells, however, a combination of low dose STZ and high fat diet has been proposed as a model for type 2 diabetes (Srinivasan, Viswanad, Asrat, Kaul, & Ramarao, 2005). Rodent animal studies of STZ alone or STZ and high fat diet-induced diabetes showed that oral administration of either ferulic acid (eight weeks, Roy, Metya, Sannigrahi, Rahaman, & Ahmed, 2013) or trigonelline (four weeks, Zhou et al., 2013) led to reduction in circulating blood glucose and lipid levels. In addition, a range of oxidative stress markers was improved in pancreatic tissue with subsequent decrease in levels of pro-inflammatory islet cytokines, beta cell apoptosis and increase in islet insulin content. This could implicate a direct effect of the compounds on the pancreatic islets. However, it cannot be excluded that the improved islet parameters were indirectly caused by a reduction of circulating stress factors (e.g. lipids) leading to localised reduction in oxidative stress levels in pancreatic tissues.

A wide range of plant polyphenols has been investigated with regard to potential beneficial effects in type 2 diabetes including assessment of underlying molecular mechanisms of action (e.g. quercetin, Carrasco-Pozo et al., 2016). There are, however, to our knowledge few studies specifically exploring the direct impact of coffee derivatives on the regulation of beta cell mass, either with regards to survival under stressful conditions typical of the development of type 2 diabetes, or concerning proliferative/hypertrophic properties of the beta cells in normal, (gluco)lipotoxic or inflammatory environments. Bhattacharya et al. (2014) mainly investigated insulin secretion *in vitro* from INS1E beta cells, but also found that caffeic acid under conditions of hyperglycaemia caused a decrease in the mRNA expression of the pro-apoptotic caspase 3 and Bax proteins and increased mRNA levels of Hsp70, suggesting a role of this particular derivative in the regulation of beta cell survival. Cheng et al. (2011) found that the detrimental effect on beta cells of amyloid polypeptide formation in type 2 diabetes (Butler, Janson, Soeller, & Butler, 2003), was decreased *in vitro* by caffeic acid and to a much lesser extent CGAs and caffeine. Similarly, Sompong et al

(2017) found that beta cell death induced *in vitro* by oxidative DNA damage was partly reversed by pre-treatment with ferulic acid – however, only at high concentrations (100 µmol/l). The scarcity of studies in this area therefore suggest that further research is needed to establish whether bioactive coffee compounds at physiologically relevant concentrations do convey protection for the beta cells, and if so, which underlying mechanisms are involved.

5. Conclusion

There is growing evidence from human studies supporting an important, protective role of coffee components in the aetiology of type 2 diabetes. This holds true for both caffeinated and decaffeinated coffee, suggesting that non-caffeine bioactives are of particular interest. Findings indicate that components such as CGA derivatives and cafestol positively modify the regulation of blood glucose levels via a number of different actions in peripheral tissues.

The impact on beta cell function is difficult to assess directly in human studies, and there is therefore a need for more mechanistic *in vitro* investigations into the role of both individual coffee components and their combinations. Some studies report on modest, but significant effects on insulin secretion although further investigations are warranted in particular with regards to use of physiologically relevant concentrations and conjugated forms of the bioactive components. Although the loss and/or dysfunction of beta cells is a key component in the development of T2D and some coffee components have been shown to have protective properties in other disease settings, very little is known specifically about the impact on factors regulating beta cell mass, including survival under conditions of hyperglycaemia, lipotoxicity and inflammation. Further and larger studies are therefore required in this field before any recommendations can be made.

Declarations of interest: None.

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Figure legend:

Figure 1: Possible mechanistic points of action for control of blood glucose by bioactive non-caffeine coffee compounds.

Glucose homeostasis is maintained via a number of insulin-dependent and independent mechanisms in peripheral tissues and in the pancreatic islets. The main mechanisms to be affected by coffee compounds (indicated in brackets) are highlighted. Inhibition of α-amylase and α-glucosidase enzymatic activity in the oral cavity and small intestine and the intestinal sodium-dependent glucose transporter (SLGT1) slows down carbohydrate digestion and glucose absorption into the circulation. Glucose uptake from the blood stream is increased by CGAs and/or derivatives in insulin-sensitive muscle and adipose tissues via upregulation of glucose transporter GLUT4. In the liver CGAs modulate expression and enzymatic activity of glucose-6-phosphatase and other components of the metabolic pathways leading to gluconeogenesis and subsequent glucose release. Insulin sensitivity in peripheral tissues is decreased by subclinical levels of circulating cytokines; however, inflammation is reduced by CGAs and metabolites. These findings are based on findings from either *in vitro* or *in vivo* studies. Please see reviews by (Santos & Lima, 2016) and (Akash, Rehman, & Chen, 2014) for more detail. In the pancreas, insulin secretion is stimulated by cafestol and potentially also CGAs and derivatives, the latter of which also reduce oxidative stress in the pancreas with subsequent increase in beta cell survival (please see text). Note that effects of coffee compounds on lipid metabolism are not included in the figure. CGAs and derivatives are collectively indicated in figure as CGAs. Schematic modified from (Guasch-Ferre, Merino, Sun, Fito, & Salas-Salvado, 2017).

Table legend:

Table 1. Estimated ranges of coffee components in green beans, roasted beans and per cup/serving, adapted from previous studies. [1](Caprioli et al., 2014), [2](Crozier et al., 2012), [3](Farah & Duarte, 2015), [4](Godos et al., 2014), [5](Heckman, Weil, & Gonzalez de Mejia, 2010), [6](Ludwig et al., 2014), [7](Maeztu et al., 2001), [8](McCusker, Goldberger, & Cone, 2003), [9](Naidoo et al., 2011), [10](Oliveira et al., 2012), [11](Poisson, Dunkel, & Hofmann, 2017), [12](Santos & Lima, 2016).

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Table

Components	Contents in green beans (% or mg/g of dry matter)	Contents in roasted beans (% or mg/g of dry matter)	Contents per cup/serving (mg/ml)
1. Carbohydrate	40-65%[11,12]	38-42%[12]	-
- Monosaccharide (e.g. fructose, glucose, galactose, arabinose, traces)	1-2%[11]	N/A[11]	-
- Oligosaccharide (e.g. Sucrose, raffinose, stachyose)	4.0-8.0%[11]	None[11]	-
- Polysaccharide (e.g. mannose, arabinose, glucose)	49.8-54.4%[11]	38-42%[11]	-
2. Nitrogen (N) containing compounds			
- Proteins	10%[11] 11%[12]	7.5%[11] 10%[2]	- -
- Caffeine	1.2-2.2%[11,12] 3.85-4.29 mg/g[4]	1.3-2.4%[11,12] 4.74-9.44 mg/g[4]	**Caffeinated coffees** **Espresso** 51-330 mg/28-50 ml [1,2,4,8] **Brew** 102-200 mg/220 ml[5] **Decaffeinated coffee** 17.7 mg/240 ml[8]
- Trigonelline	0.6-1.0%[4,6]	0.2-0.9 mg/g[6]	40-110 mg/serving[6]

3. Lipids **Diterpene** - Cafestol - Kahweol	10-16%[12] 0.045-0.19mg/g[4] 0.04-0.090 mg/g[4]	11-17%[12] *Arabica* beans = 0.3-0.7%[4] *Rusbusta* beans = ~0.1-0.3%[4] *arabica* beans = 0.1-0.3%[4] *rubusta* beans = <0.01%[4]	- **Espresso:** 0.16-2.32 mg/ 120 ml[7,9] **Filtered coffee:** 0.02 mg/150 ml[4] **Espresso:** 0.09-0.18 mg/50 ml[4] 0.16-3.12mg/120ml[7,9] **Filtered coffee:** 0.02 mg/150 ml[4]
4. Chlorogenic acids	0.8-11.9%[4]	**Commercial ground roasted coffee:** 0.003-0.035/gm[3]	**Espresso:** 96-111 mg/30 ml[7] **Filtered coffee:** 143-247mg/130 ml[7]
5. Melanoidins	None[4]	0.072 mg/g[4]	**Espresso:** 116 mg/50 ml[4] **Filtered coffee:** 270 mg/150 ml[4]
9. Minerals - Na - K - Mg - Mn	4.2-4.4%[11]	4.5-4.7%[11]	 25.9-289.4 mg/100ml[10] 3716.6-6149.6 mg/100ml[10] 306.9-546.8 mg/100ml[10] 0.99-3.99 mg/100ml[10]

Figure

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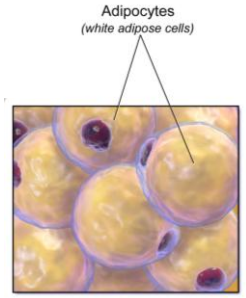
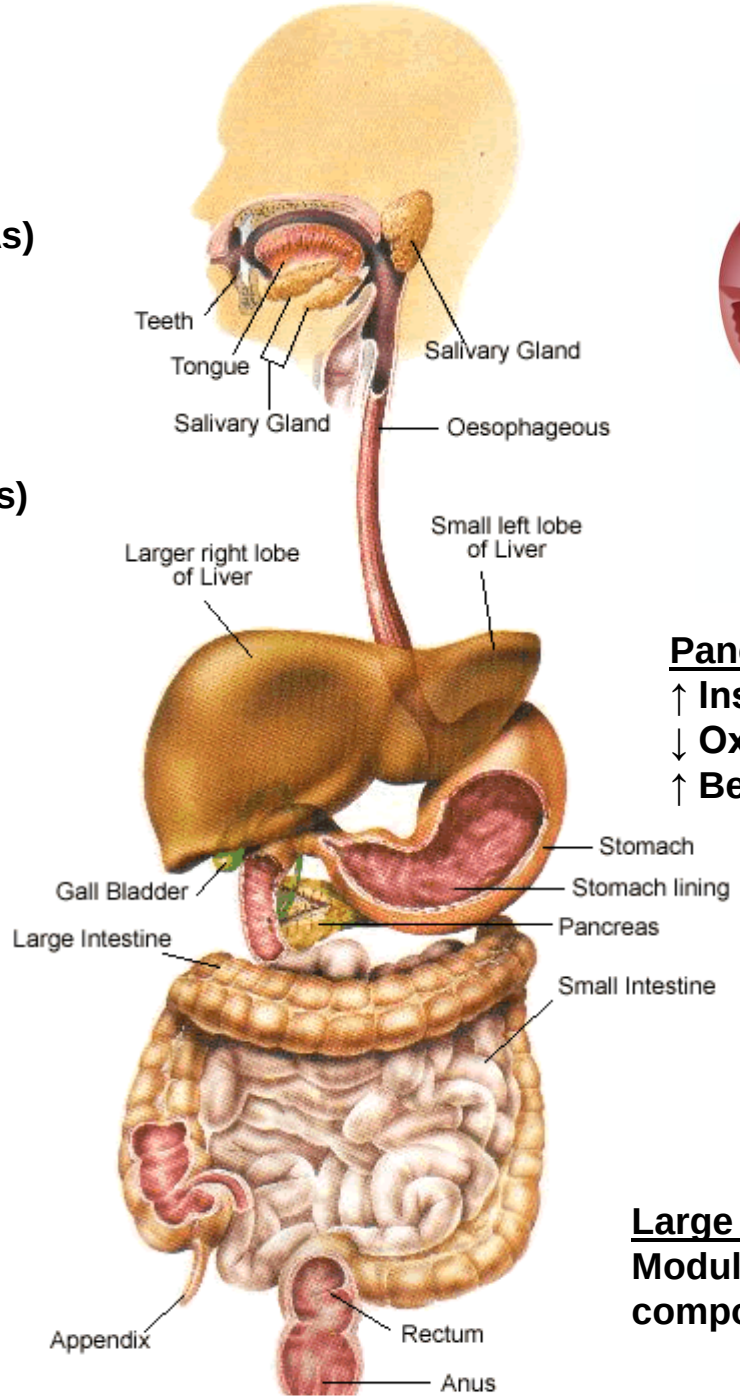
Oral cavity:
↓ α-amylase (CGAs)

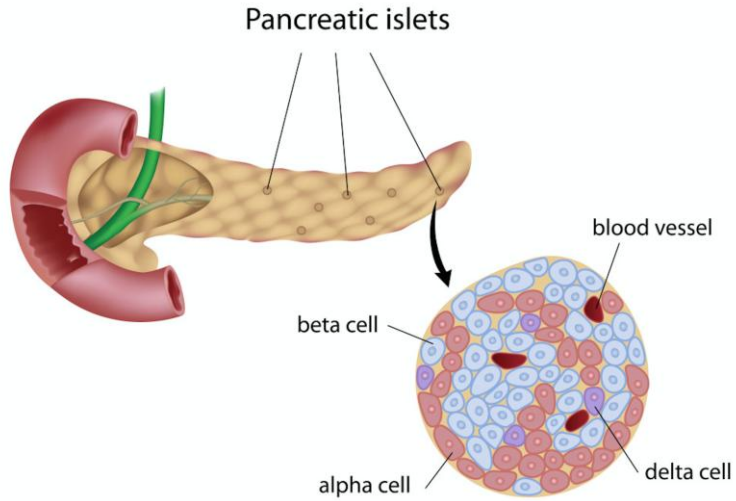
Liver:
↓ glucose-6-phosphatase (CGAs)
↓Oxidative stress (Cafestol, CGAs)
↓ Inflammation
(CGAs, trigonelline)



Adipose tissue:
↑GLUT4 (CGAs)
↓ Inflammation (CGAs)

Muscle:
↑GLUT4 translocation
(CGAs, cafestol)
↓ Inflammation (CGAs)





Pancreas:
↑ Insulin secretion (Cafestol, CGAs?)
↓ Oxidative stress (Trigonelline, CGAs?)
↑ Beta cell survival (CGAs?)

Small intestine:
↓ α-Amylase (CGAs)
↓ α-glucosidase (CGAs)
↓ SLGT1 (CGAs)

Large intestine:
Modulation of microbiota composition