Protective effects of tea, red wine and cocoa in diabetes. Evidences from human studies

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1

¹ **Abbreviations:** **AGE:** advanced glycation end products; **Apo:** apolipoprotein; **BMI:** body mass index; **BP:** blood pressure; **BW:** body weight; **Ch:** total cholesterol; **CRP:** C-reactive protein; **EC:** epicatechin; **ECG:** epicatechin gallate; **EGC:** epigallocatechin **EGCG:** epigallocatechin gallate; **FFA:** free fatty acid; **GLP-1:** glucagon-like peptide 1; **Gluc:** glucose; **GSH:** glutathione; **GTE:** green tea extract; **GTP:** green tea polyphenols, **HbA1c:** glycated haemoglobin; **HDL:** high density lipoprotein; **HOMA-IR:** homeostatic model assessment of insulin resistance; **IFN- γ :** interferon- γ ; **Ins:** Insulin; **IL-6:** interleukin-6; **IR:** insulin resistance; **LDL:** low-density lipoprotein; **MDA:** malondialdehyde; **ROS:** reactive oxygen species; **TAC:** total antioxidant activity; **T2D:** type 2 diabetes; **TG:** triglyceride; **TNF α :** tumour necrosis factor α ; **UACR:** urinary albumin-creatinine ratio.

Contents

1. Introduction
2. Physiopathology of diabetes
3. Flavanols
4. Dietary flavanols, diabetes and human studies
 - 4.1. Tea
 - 4.2. Red wine
 - 4.3. Cocoa
5. Conclusions

Conflict of interest

Acknowledgements

Abstract

Prevention of diabetes through the diet has recently received an increasing interest, and polyphenolic compounds, such as flavanols, have become important potential chemopreventive natural agents due to their proved benefits on health, with low toxicity and cost. Tea, red wine and cocoa are good sources of flavanols and these highly consumed foods might contribute to prevent diabetes. In this regard, there is increasing evidence for a protective effect of tea, red wine and cocoa consumption against this disorder. This review summarizes the available epidemiological and interventional human studies providing evidence for and against this effect. Overall observational data suggest a benefit, but results are still equivocal and likely confounded by lifestyle and background dietary factors. The weight of data indicate favourable effects on diabetes risk factors for tea, red wine and cocoa intake, and a number of plausible mechanisms have been elucidated in human studies. However, despite the growing evidence it remains uncertain whether tea, red wine and cocoa consumption should be recommended to the general population or to patients as a strategy to reduce the risk of diabetes.

Keywords: Cocoa, diabetes, dietary flavanols, red wine, tea, human studies.

Highlights

- The current state-of-the-art on diabetes and tea, red wine and cocoa consumption is reviewed.
- Epidemiologic and interventional studies mostly support a benefit of tea, red wine and cocoa intake against diabetes.
- New human studies should be encouraged to clarify the equivocal evidences before giving any recommendation to the population.
- The mechanisms behind potential tea, red wine and cocoa benefits against diabetes should be further investigated.

1.- Introduction

Diabetes mellitus is a complex metabolic syndrome, and constitutes a rising world health problem, being type 2 diabetes (T2D) the most common form of diabetes and one of the most common chronic diseases in almost all countries (Whiting, D.R. et al., 2011). This disease is characterized by hyperglycaemia, which is very commonly followed by hyperlipidaemia (Poitout, V. and Robertson, R.P., 2008). In fact, after the onset of the disease both alterations contribute to the deterioration of the pancreatic β -cell function and other tissues such as liver, muscles or adipose tissue, etc. Therefore, glucotoxicity and lipotoxicity should be taken into account in T2D, as both hyperglycaemic and hyperlipidaemic abnormalities exert damaging or toxic effects in different tissues of the organism and are also responsible for the serious health complications associated to this disease (cardiovascular disease, kidney failure, blindness, neuropathy, etc.) (Chaturvedi, N., 2007).

Due to the relevance of T2D, many drugs have been developed trying to ameliorate or cure this disease, although the current medications are not sufficiently effective in maintaining long-term glycaemic control in a high percentage of patients. Indeed, at present it is considered that the most efficient approach to prevent or delay the onset of diabetes at the lowest cost is at nutritional level (Dembinska-Kiec, A. et al., 2008). Then, the identification of dietary components as potential antidiabetic agents has become an essential subject in the current research. In this regard, polyphenols, which are present in fruits and vegetables, have attracted a great deal of interest because of their potential ability to act as highly effective chemopreventive agents (Dembinska-Kiec, A. et al., 2008). Indeed, tea, red wine and cocoa are good sources of flavanols (a class of polyphenol), but it is not completely established whether these foodstuffs exert a beneficial effect against diabetes. Therefore, the present review is focused on

describing the current evidence on the link between tea, red wine or cocoa consumption and diabetes, based on epidemiologic and interventional studies in humans.

2.- Physiopathology of diabetes

Hyperglycaemia, which is the biochemical hallmark of T2D, results from a combination of genetic and acquired factors. The main pathophysiologic features driving T2D are peripheral insulin resistance (IR) and eventual destruction of insulin producing beta-cells in pancreas (Guillausseau, P.J. et al., 2008). Although IR, which is characterised by high circulating levels of glucose and insulin, is the earliest detectable abnormality of T2D, it has been pointed that changes in insulin secretion determine both the onset of hyperglycaemia and the progression toward insulin therapy (Marchetti, P. et al., 2012). Actually, during IR beta cells maintain normal glucose tolerance by increasing insulin output, but when beta cells cannot secrete adequate amounts of insulin to cope with IR chronic hyperglycaemia appears. At the early stages of the illness, hyperglycaemia increases gradually but patients do not notice any classic symptom; therefore, T2D usually remains undiagnosed for many years. Together with hyperglycaemia, elevations of plasma free fatty acid (FFA) levels that often accompany insulin resistance, also play a pathogenic role in the early stages of the disease (Poitout, V. and Robertson, R.P., 2008). Once the primary pathogenesis of diabetes is established, hyperglycaemia and very commonly hyperlipidaemia exert additional damaging or toxic effects (glucotoxicity and lipotoxicity, respectively) in a variety of tissues including beta cells and those involved in insulin resistance leading to the progression of T2D (Poitout, V. and Robertson, R.P., 2008).

The pathogenic effect of hyperglycaemia, in concert with FFA release, is mediated to a significant extent via increased generation of intracellular reactive oxygen species

(ROS). Several pathways are identified in the literature as major contributors of ROS production in the organism: activation of polyol pathway flux, increased formation of advanced glycation end products (AGEs), increased expression of AGEs receptor and its activating ligands, activation of protein kinase C and excessive activity of the hexosamine pathway (Robertson, R.P., 2004). ROS can directly inflict damage on macromolecules and can also indirectly lead to tissue damage by activating a number of cellular stress-sensitive pathways. Accordingly, beta cells are especially vulnerable to ROS because of its low intrinsic level of antioxidant enzymes (Robertson, R.P., 2010). Chronically excessive ROS levels cause decreased insulin gene expression, content and secretion and also accelerate rates of apoptosis contributing to the inexorable decrease of beta cell mass and functionality (Robertson, R.P., 2004). Similarly, oxidative stress is believed to modify a number of signalling pathways within the cell that can ultimately provoke insulin resistance. In particular, elevated ROS production inhibits insulin signalling in peripheral tissues leading to the inability of insulin to increase glucose disposal and to suppress glucose production. Altogether, these effects significantly accelerate the development of the disease (Bashan, N. et al., 2009).

Oxidative stress has also been implicated in the progression of diabetic complications. Increase in ROS levels is associated with long-term dysfunction and failure of various organs, especially eyes, kidneys and nerves (Wei, W. et al., 2009). Interestingly, the vascular endothelium has been identified as an most important component in diabetes-associated complications, which include many cardiovascular disorders such as atherosclerosis, hypertension and peripheral neuropathy. Increased ROS levels impair endothelial nitric oxide synthase activity resulting in diminished nitric oxide bioavailability and vascular endothelial dysfunction (Kolka, C.M. and Bergman, R.N., 2013). Intrinsic properties of the injured endothelium result in vasoconstriction, smooth

cell proliferation, coagulation disorders, leukocyte aggregation, thrombosis, and vascular inflammation predisposing to atherosclerosis (Versari, D. et al., 2009). Therefore, biomarkers of endothelial dysfunction, such as vascular cell adhesion molecule-1, and markers of systemic inflammation including C-reactive protein (CRP) and tumour necrosis factor (TNF)- α are pathologically enhanced in diabetic subjects (Tousoulis, D. et al., 2013).

Currently there are different classes of antidiabetic agents approved for the management of T2D. However, the usage of these drugs is often associated with serious undesirable side effects, including weight gain, hypoglycaemia and gastrointestinal disturbances (He, Z.X. et al., 2015). Considering the importance of ROS and oxidative stress in the aetiology of diabetes and its complications, one of the main challenges of research in recent years has been to identify natural dietary compounds that can attenuate oxidative stress. Accordingly, several findings suggest the potential use of phenolic compounds, with demonstrated pharmacological properties, as a potential strategy to prevent the development and the progression of diabetes and its associated complications (Del Rio, D. et al., 2013). In this context, tea, red wine and cocoa have received much attention because they are particularly rich in flavanols, a main class of polyphenols with strong antioxidant properties.

3.-Flavanols

Flavanols belong to the chemical family of polyphenols and they are a class of flavonoids. Flavanol molecular structure consists of two benzene rings joined by a linear three-carbon chain that forms an oxygenated heterocycle (C6–C3–C6) and contains a saturated three-carbon chain with a hydroxyl group in C3 (Ramos, S., 2008).

Flavanols are abundant in cocoa, tea, red wine, grapes and apples, among the richest sources (Manach, C. et al., 2004). Flavanols exist as monomers and polymers, and they are named as catechins and proanthocyanidins, respectively. The main representative flavanols in fruit are catechin and (-)-epicatechin (EC), whereas (-)-epigallocatechin gallate (EGCG), (-)-epigallocatechin (EGC), and (-)-epicatechin gallate (ECG) are found especially in tea (Manach, C. et al., 2004) (Figure 1). Unlike other classes of flavonoids, flavanols are not glycosylated in foods (Manach, C. et al., 2004).

Catechins are found in many fruits such as apricots (250 mg/Kg fresh weight) and cherry (250 mg/Kg fresh weight), although the richest sources are green tea (up to 800 mg/L), chocolate (up to 600 mg/L), and red wine (up to 300 mg/L). In addition, proanthocyanidins, also known as condensed tannins, are dimers, oligomers, and polymers of catechins, and are responsible for the astringent character of fruits (grapes, apples, berries, etc.) and beverages (tea, wine, cider, beer, etc.) and for the bitterness of cocoa (Rasmussen, S.E. et al., 2005). Proanthocyanidins have a wide range of structures and molecular weights and their degree of polymerization could be higher than 10 (Aron, P.M. and Kennedy, J.A., 2008). However, due to analytical limitations, the only available data for proanthocyanidins are reported as total-phenols or catechins or dimers and trimers (Aron, P.M. and Kennedy, J.A., 2008).

Upon intake, monomeric flavanols and certain dimeric procyanidins are absorbed in the small intestine via passive diffusion, and rapidly yielding sulfate, glucuronide, and methylated sulfate/glucuronide metabolites through the respective actions of sulfotransferases, uridine-5-diphosphate glucuronosyltransferases, and catechol-O-methyltransferases (Aron, P.M. and Kennedy, J.A., 2008). Thus, their metabolites are rapidly detected in plasma and urine (Baba, S. et al., 2000, Holt, R.R. et al., 2002, Roura, E. et al., 2005, Tsang, C. et al., 2005). Once absorbed, the non-metabolized

flavanol rapidly undergoes glucuronidation, sulfation, and O-methylation in the liver, and a degree of enterohepatic recirculation could take place with certain elimination of the flavanol via the bile (Actis-Goretta, L. et al., 2013). In addition, procyanidins that are poorly absorbed in the gastrointestinal tract (Manach, C. et al., 2005, Serra, A. et al., 2010), are metabolized together with monomeric flavanols in the large intestine by the gut microbiota, and they are absorbed and further metabolized in the liver prior to their renal excretion. Thus, after the intake of flavanol-rich food (cocoa, tea, red wine, etc.) various polyphenol-derived phenolic acids, such as m-hydroxyphenylpropionic acid, m-hydroxyphenylacetic acid, and m-hydroxybenzoic acid, as well as phenyl- γ -valerolactones are generated (Spencer, J.P.E., 2003, Stockley, C. et al., 2012, Urpi-Sarda, M. et al., 2009). Indeed, these phenolic metabolites have been recently shown to possess an anti-diabetic potential by *in vitro* studies (Martín, M.A. et al., 2016).

4.-Dietary flavanols, diabetes and human studies

4.1.-Tea

Tea is considered one of the most widely consumed beverages in the world, only second to water. Tea is generally divided into three types according to the degree of fermentation: green tea (non-fermented), oolong tea (semi-fermented) and black tea (fermented). The fresh tea leaves contain caffeine (approximately 3.5% of the total dry weight), theobromine (0.15-0.2%), theophylline (0.02-0.04%) and other methylxanthines, lignin (6.5%), organic acids (1.5%), chlorophyll (0.5%) and other pigments, theanine (4%) and free amino acids (1-5.5%), and numerous flavour compounds (Graham, 1992). In addition, a wide variety of other components exists, including, flavones, phenolic acids, carbohydrates, minerals, vitamins, alkaloids, and enzymes (Chaturvedula, V.S.P. and Prakash, I., 2011). In this line catechins are the

most abundant polyphenols in green tea, and usually account for 30-42% of the dry weight of the solids in brewed green tea (Balentine, D.A. et al., 1997). The four major catechins in tea are EGCG, EGC, ECG and EC; indeed, EGCG is the major catechin in tea and may account for 50-80% of the total catechins in tea. Gallocatechin gallate, gallocatechin, catechin gallate, catechin, epigallocatechin digallates, epicatechin digallate, 3-O-methyl EC, 3-O-methyl EGC, and afzelechin are present in smaller quantities (Balentine, D.A. et al., 1997). The main pigments in black tea are theaflavins and thearubigins, which are formed by the oxidation and polymerization of catechins during the fermentation; indeed thearubigins account for up to 60% of the dry weight of black tea extract (Balentine, D.A. et al., 1997).

Flavonols, including quercetin, kaempferol, myricetin, and their glycosides (mono-, di-, and tri-), are also present in tea, and constitute about 0.5-2.5% (w/w) extract as aglycone in tea infusions (Balentine, D.A. et al., 1997). Apigenin, the only flavone identified in tea, and its glycosides have also been detected but represent a very small fraction of the tea polyphenols (Balentine, D.A. et al., 1997).

In recent years, tea consumption has been extensively studied in relation to various diseases, including diabetes, and there is rising evidence that tea may prevent diabetes (Babu, P.V.A. et al., 2013, Pastoriza, S. et al., 2017). Several meta-analyses have reported that tea consumption may lower the risk of T2D, and it has been suggested a daily intake of ≥ 4 cups (Huxley, R. et al., 2009, Jing, Y. et al., 2009, Yang, J. et al., 2014, Yang, W.-S. et al., 2014). According to that, some epidemiologic studies have showed an inverse association between tea consumption and T2D risk (Table 1). In the EPIC study, a prospective cohort of 38,176 participants, a total intake of at least three cups of tea per day was associated with a reduced risk of T2D (van Dieren, S. et al., 2009). Similarly, in the National Health and Nutrition Epidemiologic Follow Up Study

(NHEFS), which is a longitudinal follow-up study of 14,407 people aged 25-74 years, a negative relationship between diabetes risk and consumption of regular tea was observed, but only in non-elderly adults (≤ 60 years) who had previously lost weight (Greenberg, J.A. et al., 2005). Furthermore, data from the Mediterranean Islands (MEDIS) epidemiologic study, in which participated 234 men and 308 women (aged 65-100 years), 54% of participants drank 1-2 cups/day, and it was detected an inverse association between tea consumption and reduced levels of fasting blood glucose, but only among non-obese elderly people (Polychronopoulos, E. et al., 2008). Also in support of the anti-diabetic effect of tea in a retrospective cohort study carried out in Japan with 17,413 participants (6,727 men and 10,686 women, 40-65 years) (Iso, H. et al., 2006) the consumption of green tea was inversely associated with the risk for diabetes after adjustment for age, sex, body mass index, and other risk factors, although no relationship was found between consumption of black or oolong teas and the risk for diabetes (Iso, H. et al., 2006). Additionally, a modest inverse relationship was observed between T2D and intake of tea in the randomized, double-blind, placebo-controlled trial Women's Health Study (WHS) with 38,018 participants (Song, Y. et al., 2005); indeed, a decreased risk of diabetes when tea consumption was ≥ 4 cups/day was reported. However, in non-diabetic women (344 participants) total intake of flavonols and flavones was not related to plasma concentrations of fasting insulin, haemoglobin A1c (HbA1c), CPR, or interleukin (IL)-6 (Song, Y. et al., 2005).

Nevertheless, some epidemiologic studies have failed to show a beneficial impact of tea consumption on the risk for diabetes. The prospective cohort in the Singapore Chinese Health Study (36,908 participants aged 45-74 years) described that regular consumption of black tea, but not green tea, was only potentially associated with lower risk of T2D in Asian men and women in Singapore (Odegaard, A.O. et al., 2008). Also in this line, the

study with Whitehall II cohort (10,308 participants, aged 35-55) reported that moderate intake (more than three cups per day) of tea was not prospectively associated with incidence of T2D, although there was evidence of a combined effect between tea and coffee consumption (Hamer, M. et al., 2008). Similarly, no relationship was observed between tea consumption and the risk of diabetes in a cohort in Takayama, Japan (31,152 participants, aged 35 years) (Oba, S. et al., 2010). Finally, one study has shown a negative effect of tea intake on the risk of diabetes. In a prospective cohort study in Japanese men, long-term high oolong tea consumption (2 or more cups per day) was associated with a higher risk of T2D, as an increment in fasting blood glycaemia was detected (Hayashino, Y. et al., 2011).

Since the relationship between tea consumption and risk of T2D from epidemiologic evidence is still equivocal, intervention studies have been encouraged to clarify this aspect and to elucidate the mechanisms of action. In this regard, Ma et al. (2015) have demonstrated that patients with diabetic retinopathy who had regularly drunk Chinese green tea every week for at least one year had a reduced risk of this disease (around 50%) (Table 2). In this study 100 diabetic patients with retinopathy and 100 age-sex-matched diabetic controls without retinopathy (aged ≥ 18 years) were asked whether they drank green tea every week at least for one year and they were defined as “regular Chinese green tea drinkers”, and when stratified by sex, the protective effect of Chinese green tea consumption on diabetic retinopathy was significant in women, but not in men. Similarly, an improvement in non-receiving insulin diabetic patients after the intake of a catechin-rich beverage for 12 weeks was observed in a double-blind controlled study (Nagao, T. et al., 2009). Japanese patients with T2D ingested green tea containing either 582.8 mg of catechins (catechin group; n=23, 63-66 years) or 96.3 mg of catechins (control group; n=20, 60-65 years) per day for 12 weeks. At the end of the

study, the catechin group showed a decrease in waist circumference and increased adiponectin levels. Insulinaemia also increased at week 12 in the regular green tea consumers, but no difference was noted between the two groups in glycaemia and HbA1c values. Additionally, in patients treated with insulinotropic agents, the enhancement of the insulinaemia after 12 weeks was higher in participants receiving the catechin-rich beverage than in the control group, which might indicate a recovery of the insulin-secretory ability (Nagao, T. et al., 2009). Beneficial effects on blood pressure (BP) have also been observed in two randomized clinical trials (Mousavi, A. et al., 2013, Mozaffari-Khosravi, H. et al., 2013). Mousavi et al. (2013) included 63 patients with T2D (30 males and 33 females, aged 35-65 years) who were randomly assigned into three groups depending on the daily intake of green tea as follows: four cups of green tea per day (n = 24), two cups of green tea per day (n = 25), and the control group (n = 14) with no green tea intake for two months. Green tea was prepared using 2.5 g tea bags in 200 mL of boiled water for 5 minutes. Consumption of four cups of green tea per day decreased the systolic BP, and also body weight, body mass index (BMI) and waist circumference. However, no significant differences were found in the serum fasting blood glucose levels or lipid profiles, including, serum total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, apolipoprotein A1 (Apo A1), and Apo B100, as well as in the serum total antioxidant capacity and malondialdehyde (MDA) levels after the two months of intervention (Mousavi, A. et al., 2013). Similarly, a decrease in systolic and diastolic BP was detected in 100 mildly hypertensive patients (age ranged between 30 to 60 years) that received a green tea infusion three times per day 2 h after each meal for 4 weeks (Mozaffari-Khosravi, H. et al., 2013). In this case, green tea was prepared by boiling 3-g green tea bags in 150 mL of water for 5 minutes. Also the administration of a green tea

extract (500 mg in one capsule 30 minutes after meals three times daily for 16 weeks) to 92 patients with T2D (20-65 years) decreased triglyceride levels, homeostasis model assessment of insulin resistance index (HOMA-IR), and increased high HDL cholesterol, adiponectin, Apo A1, Apo B100 and glucagon-like peptide 1 (GLP-1) (Liu, C.-Y. et al., 2014).

As mentioned above, green tea might also exert beneficial effects on diabetic complications. Thus, in a randomised, double-blind, placebo-controlled clinical trial with 42 diabetics with a urinary albumin-creatinine ratio (UACR) >30 mg/g, patients received either four capsules of green tea polyphenols (corresponding to 800 mg of EGCG, n=21) or placebo (n=21) for 12 weeks, and it was reported a decrease in UACR by 41% in the green tea polyphenol-group (Borges, C.M. et al., 2016). Additionally, the administration of a green tea extract (500 mg in one capsule after the meal three times a day for 8 weeks) to 72 patients with T2D (≥ 40 years) diminished fasting blood glucose, fasting insulin and HbA1c levels, and improved bone turnover (Mirzaei, K. et al., 2009). The number of studies performed with black or oolong tea is lower than those with green tea, but certain works have also shown beneficial effects on diabetes for those types of teas. In this line, Neyestani et al. (2010) have reported a decrease in serum MDA values with a daily intake of two cups of black tea, and a diminution in serum CPR values and increase in glutathione levels with a consumption of 4 cups per day. In this study, black tea was prepared by boiling a 2.5 g tea bag in 150 mL of water for 2 minutes, and 46 patients with T2D were randomly assigned to either the test (n = 23) or the control (n = 23) group. In the test group, daily intake of black tea was increased by 150 mL (1 cup) each week, to 300, 450 and 600 mL in weeks 2, 3 and 4, respectively. The control group was asked to stay on 150 mL/day of black tea throughout the intervention period (Neyestani, T.R. et al., 2010). Likewise, the administration of 3

cups/day (600 mL, high intake) or one cup/day (200 mL, low intake) of black tea to 36 patients with T2D (18 men and 18 women) for 12 weeks showed certain improvements related to the disease in the high-intake-patients (Mahmoud, F. et al., 2016). Thus, in the tea-group it was observed reduced HbA1c and total serum cholesterol levels, along with increased regulatory T cells CD3+ CD4+ CD25+ FOXP3, CD3+ CD4+ IL-10+ cells (an immunosuppressive phenotype), reduced (pro-inflammatory) CD3+ CD4+ IL-17+ cells and reduced Th1-associated CD3+ CD4+ IFN- γ + cells. The preparation of tea was as follows: one tea bag as (2.5 g) of dry black tea as sold was infused in 200 mL of water brought to a boil, then steeped for 3 minutes (Mahmoud, F. et al., 2016). Finally, an study with oolong tea demonstrated that the consumption of 1,500 mL oolong tea [five tea bags (15 g of tea leaf) were added to 1,500 mL of boiling water and steeped for 10 minutes] taken five times per day independent of daily water intake for 30 days diminished the glycaemia and plasma fructosamine levels (Hosoda, K. et al., 2003). This randomized crossover design included 20 patients (10 women and 10 men) with an average age 61.2 years.

On the contrary, other studies have reported a lack of effect after the administration of tea. Ryu et al. (2006) described that 55 T2D patients (31 men and 24 women, aged 46-62 years) that received 900 mL water containing 9 g of green tea per day for 4 weeks did not change blood glucose, blood insulin, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), insulin resistance, or serum adiponectin levels, as well as inflammatory markers, such as CRP, IL-6 or brachial-ankle pulse wave velocity. Similar results were obtained after administering a fraction of green tea extracts/powder containing 544 mg polyphenols (456 mg catechins) after every meal or snack for 2 months to 66 patients aged 32-73 years (53 males and 13 females) with borderline diabetes or diabetes (Fukino, Y. et al., 2005). In addition, the daily

supplementation with green tea polyphenols did not modify the body weight, BMI, systolic and diastolic blood pressures, blood glucose, HbA1c, or insulin values, as well as HOMA index. In the same line, the daily supplementation with 1,500 mg of a decaffeinated green tea extract to 68 obese type 2 diabetics (20-65 years) for 16 weeks did not reduce HbA1c levels, waist circumference, HOMA-IR index, insulin levels, and enhanced ghrelin values when compared the green tea and placebo groups, although those differences were observed within the group receiving the green tea extract in comparison to the baseline (Hsu, C.H. et al., 2011). Finally, in a double-blind, placebo-controlled, randomized multiple-dose (0, 375, or 750 mg per day for 3 months) study in which an extract of green and black (40% catechins from green tea and 20% theaflavins from black tea) tea was administrated to 49 adults (average age of 65 years) with T2D, no differences were found in the levels of HbA1c among groups (MacKenzie, T. et al., 2007).

As pointed above, caffeine might have an effect in diabetes; indeed, several epidemiologic studies have identified an inverse association between habitual coffee and tea consumption, major sources of caffeine, and T2D (Huxley, R. et al., 2009). However, short-term metabolic studies have shown that caffeine increases blood glucose concentrations and decreases insulin sensitivity (Robinson, L.E. et al., 2004). Bhupathiraju and coworkers (2013) prospectively evaluated the association of both caffeinated and decaffeinated coffee and tea consumption on the risk of T2D in two large cohorts of American men and women (74,749 women from the Nurses' Health Study and 39,059 men from the Health Professionals Follow-Up Study). It was reported that caffeinated tea lowered the risk of T2D among women, but this was not observed for decaffeinated tea or among men, and that coffee intake was associated with a

reduced risk of T2D. All together indicates that the role of caffeine in diabetes is still controversial and that more trials with longer follow-up are needed.

Despite both *in vitro* and *in vivo* studies seem to indicate that tea possesses antidiabetic effects (Pastoriza, S. et al., 2017), its mechanism of action remains unclear. In this line, it has been suggested that the beneficial effects of tea on T2D are related to its antioxidant capacity, as well as to the modulation of signals involved in the modulation of oxidative stress, and in the insulin pathway, inhibition of digestive enzymes (α -amylase and α -glucosidase activity), improvement of endothelial dysfunction, and modulation of inflammation (cytokine expression) (Pastoriza, S. et al., 2017). However, these promising results are in contrast with the equivocal relationship showed in humans. These disagreements could be related to the different chemical composition of teas, which varies with the cultivars and as well as to the degree fermentation during tea leaves processing, as green tea contains higher amounts of polyphenols when compared to oolong and black tea (Balentine, D.A. et al., 1997), and the way of tea preparation (amount in tea bags, time in boiling water, volume of water, etc.). In addition, differences in bioavailability of tea components due to different physiological status between individuals and populations should also be considered. Therefore, additional human studies should be encouraged in which all possible variables were well defined and in which long-term habitual consumption should also be examined.

4.2.-Red wine

Wine is a beverage with a wide variety of chemical components. Water is the predominant constituent followed by ethanol, carbon dioxide, glycerol, sugars, polysaccharides, higher alcohols, acids and phenolic compounds (Stockley, C. et al., 2012). The phenolic compounds found in wine include flavonoids (85%) such as

flavanols, flavonols and anthocyanins and non-flavonoid compounds like phenolic acids, phenols and stilbenes. Interestingly, red wine contains 10-fold more phenolic compounds than white wine (Stockley, C. et al., 2012). It is commonly accepted that wine, and especially red wine, has a positive effect on organs and systems (Artero, A. et al., 2015). In addition, many reported health-promoting activities associated to red wine consumption have been positively correlated with their flavonoid compounds composition (Fernandes, I. et al., 2017).

Over the last decade, several epidemiological studies have observed that moderate intake of wine, defined as up to 1 drink per day for women and up to 2 drinks per day for men, is associated with a lower risk of T2D (Table 3). According to that, in 2006, a prospective study of 36,527 adults aged 40-69 at baseline from Australia (Hodge, A.M. et al., 2006) concluded that wine consumption was associated with reduced risk of T2D. Likewise, Beulens et al. 2012) in the European Investigation into Cancer and Nutrition (EPIC)-InterAct study including over 12,000 incident cases of T2D in eight European countries, confirmed that moderate alcohol consumption is associated with a reduced risk of T2D. Cullmann et al. (2012) examining the possible association between different alcoholic beverages and the risk of diabetes in a Swedish population determined that medium wine intake reduced the risk of pre-diabetes and T2D in women. Besides, in the Nord-Trøndelag Health Survey (HUNT) study, moderate wine consumption rather than beer and spirits was associated with reduced risk of both T2D and autoimmune diabetes (Rasouli, B. et al., 2013). More recently, Fagherazzi et al. (2014) evaluated for the first time the associations between T2D risk and both baseline wine consumption and trajectories of wine consumption frequency throughout life. A total of 66,485 women from the French prospective Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale (E3N)-EPIC cohort were

followed between 1993 and 2007; 1,372 incident cases of T2D were diagnosed during the follow-up. In this study, wine drinking was inversely associated with T2D risk but only in overweight women, who would already be at higher risk of T2D. Marques-Vidal et al. (2015) using the Caucasian population of Lausanne (Switzerland) study (Colaus Study), conclude that no specific alcoholic beverage protects from T2D or impaired fasting glucose, with the possible exception of a protective effect of wine consumption on T2D. Recently, a systematic review and meta-analysis of 13 prospective studies, enrolling 397,296 participants and 20,641 cases of T2D, has explored the relationship between the specific types of alcoholic beverages and the incidence of T2D. The results of this meta-analysis showed that wine consumption is associated with a robust significantly decreased risk of T2D (Huang, J. et al., 2016). More interestingly, a recent prospective study has shown that diabetic patients who reported moderate drinking presented decreased risks of cardiovascular accidents, micro vascular complications as well as all-cause mortality and this beneficial association was especially strong for predominantly wine drinkers (Blomster, J.I. et al., 2014).

Results of epidemiologic studies have stimulated the development of human interventional trials to establish causality and to elucidate the underlying mechanisms (Table 4). In this regard, Napoli et al. (2005) studied a group of 17 T2D patients treated with diet alone or with low doses of oral hypoglycaemic agents (sulphonylureas and/or metformin). One group of 9 patients, started the daily ingestion of 180 mL of red wine at lunch and dinner (wine-treated diabetics) during two weeks and a second group of 8 diabetic patients continued their usual diet without any alcoholic beverage (control diabetics). Two weeks later, insulin-mediated whole-body glucose disposal improved by 43% after red wine consumption but did not change in the control group, suggesting that red wine attenuates insulin resistance. Similarly, Chiva et al. (2013) investigated the

effect of red wine polyphenols and alcohol on glucose metabolism and the lipid profile in 68 subjects at high cardiovascular risk, 16 of who were diabetic. The subjects received either red wine (30 g alcohol/day), the equivalent amount of dealcoholized red wine, and gin (30 g alcohol/day) for 4 week periods. The mean adjusted insulin values decreased significantly after the red wine and dealcoholized red wine interventions leading to the conclusion that red wine rich in polyphenols with or without alcohol significantly improves insulin sensitivity. They also observed that fasting glucose concentrations did not change in any intervention. Nevertheless, Shai and colleagues (2007), in a randomized control trial, assessed the effect of daily moderate alcohol intake (150 mL of wine) in 109 patients with T2D on glycaemic control in the fasting and postprandial states. Fasting plasma glucose was found to decrease after three-month of wine consumption and those patients with higher baseline haemoglobin glycosylated levels appeared to benefit more. Interestingly, the results also showed that initiating moderate daily alcohol consumption in T2D patients caused no notable adverse effects or changes in liver function biomarkers during the 3-month intervention. Similarly, another study evaluating the effect of 30-day moderate wine consumption (120 to 240 mL) indicated non-adverse effects on body weight, BP, plasma lipids or episodes of mild hypoglycaemia in T2D subjects (Bantle, A.E. et al., 2008).

Marfella et al. (2006), in a long-term controlled study randomized 115 subjects with diabetes who had sustained a first non-fatal myocardial infarction to receive (intervention group) or not (control group) a moderate daily amount of red wine (118 mL) during 1 year. At the end of the study, moderate consumption of red wine with meals in diabetic patients was associated with a significant reduction in oxidative stress and inflammatory markers and improvement of cardiac function. These findings were also supported by a long-term randomized controlled trial with 224 well-controlled

diabetic patients in Israel (2-year CASCADE Study-CARDiovaSCuLAR Diabetes & Ethanol-) (Gepner, Y. et al., 2015). This study suggests that initiating moderate wine intake (150 mL/day), especially red wine, as part of a healthy diet is apparently safe and modestly decreases cardiometabolic risk. Moreover, in the same 2-year randomized controlled intervention trial, Golan et al. (2017) found that moderate red wine consumption, combined with a healthy diet, was not likely to cause a deterioration in the proportion of abdominal adipose fat and did not promote weight gain.

The exact mechanism for the beneficial effect by which wine may protect against the development of T2D is still unclear. One suggested mechanism is just the protection against oxidative-nitrative stress exerted by the non-alcoholic fraction of red wine containing polyphenols (Robertson, R.P., 2014). In the same line, the beneficial effect of wine consumption in the development of diabetic complications seems to be also related to the ability of polyphenols to reduce oxidative stress (Robertson, R.P., 2014). Finally, the non-alcohol bioactive compounds from wine could also modulate glucose and lipid metabolism and insulin sensitivity (Fernandes, I. et al., 2017). However, further intervention studies are essential to clarify conflicting findings and to confirm or refute the anti-diabetic effects of dietary polyphenols from wine.

4.3.-Cocoa

Cocoa and its derivative products are widely consumed worldwide, and constitute a large proportion of the diet of many individuals, comparable to that of green tea, wine, or soy beans (Lee, K.W. et al., 2003, Tabernero, M. et al., 2006). Cocoa is a rich source of proteins (15-20%), carbohydrates (15%), fibre (26-40%) and lipids (10-24%), minerals (Ca, K, Mg), vitamins (A, B, E) and methylxanthines (theobromine and caffeine) (Kim, J. et al., 2014). Cocoa also contains high amounts of phenolic

compounds, such as monomer flavanols EC, and (+)-catechin, as well as procyanidins, especially dimer procyanidin B2 and B1, which are the most abundant phytochemicals in cocoa (Rusconi, M. and Conti, A., 2010). Other polyphenols such as flavonols (quercetin, isoquercitrin, hyperoside, etc.), flavones (luteolin, apigenin), flavanones (naringenin), anthocyanins and phenolic acids are present in lower amounts in cocoa (Martín, M.A. et al., 2016). In fact, cocoa is the food that has the highest flavonoid content on a per-weight basis and this seems to be related to its health effects (Martín, M.A. et al., 2016).

Systematic reviews and meta-analyses (Buitrago-Lopez, A. et al., 2011, Ellam, S. and Williamson, G., 2013, Grassi, D. et al., 2015, Hooper, L. et al., 2012, Martín, M.A. et al., 2016, Shrive, M.G. et al., 2011, Vitale, M. et al., 2016, Zamora-Ros, R. et al., 2014) are consistent with positive effects of cocoa and dark chocolate on improving insulin resistance, endothelial function, BP and/or lipid profile. Another recent meta-analysis of randomized controlled trials showed that cocoa flavanol intake significantly improved insulin sensitivity and lipid profile (Lin, X. et al., 2016). Furthermore, the most recent meta-analysis of prospective studies has concluded that chocolate intake in moderation (≤ 6 servings/week) is associated with decreased risks of coronary heart disease, stroke, and diabetes (Yuan, S. et al., 2017). Several intervention studies and prospective observations in longitudinal studies have led to similar conclusions and a number of potential mechanisms have been postulated to explain the expected benefits of cocoa and dark chocolate for diabetics (Grassi, D. et al., 2013, Mellor, D.D. et al., 2015, Strat, K.M. et al., 2016).

Regarding recent epidemiological evidence, latest results suggest that long-term consumption of any kind of chocolate may evoke an inverse relation with occurrence of T2D in younger and normal-body weight men (Matsumoto, C. et al., 2015). Early this

year, two large studies have shown ambiguous support to chocolate in T2D. In a more than 30 year-long prospective, a moderate chocolate intake of several times per week may be related to the reduction of the incidence (new cases) of T2D (Crichton, G.E. et al., 2017). However, in a long-term prospective cohort study in American women, Greenberg et al. concluded that long-term intake of any kind of chocolate is unlikely to reduce the risk of T2D in postmenopausal women (Greenberg, J.A. et al., 2017).

Regarding intervention studies with chocolate (Table 5), in a series of pioneering reports, administration of flavanol-rich dark chocolate (500 mg polyphenols/day) decreased BP, lowered insulin resistance and increased insulin sensitivity in healthy volunteers (Grassi, D. et al., 2005a). Similar results were reported in hypertensive subjects with glucose intolerance that received dark chocolate (Grassi, D. et al., 2005b) and hypertensive subjects without glucose intolerance that received dark chocolate containing 1080 mg of total polyphenols/day (Grassi, D. et al., 2008). In these two latter studies, dark chocolate decreased BP and HOMA-IR, increased insulin sensitivity, and increased β -cell function as compared to white chocolate. In a longer intervention with diabetic patients, Mellor and colleagues (2010) showed that the ingestion of a high-polyphenol chocolate providing 50 mg of epicatechins during 8 weeks was effective in improving the atherosclerotic cholesterol profile without affecting body weight, IR, BP or glycaemic control. A later study demonstrated that a 4 week consumption of dark chocolate containing 500 mg polyphenols by lean and overweight females reduces BP and improves glucose regulation as indicated by the reduction in fasting glucose and HOMA-IR (Almoosawi, S. et al., 2012). Further, in a long study undertaken in the United Kingdom (the FLAVO study) (Curtis, P.J. et al., 2013, Curtis, P.J. et al., 2012), the combined intake of chocolate enriched in flavanols and isoflavones by statin-treated diabetic women resulted in improvements in lipoprotein status and a significant

reduction of insulin resistance. Finally and more recently, administration of high-cocoa polyphenol-rich chocolate improved BP in patients with diabetes and hypertension (Rostami, A. et al., 2015).

Regarding intervention studies with cocoa (Table 6), consumption for 12 weeks of a high-flavanol cocoa diet (902 mg flavanols/day) by overweight and obese adults significantly enhanced endothelial function, reduced IR and diastolic and mean arterial BP as compared to individuals that consumed a low-flavanol cocoa diet (Davison, K. et al., 2008). More recently, EC-rich cocoa mediated modulation of oxidative stress regulators in skeletal muscle of heart failure and T2D patients (Ramírez-Sánchez, I. et al., 2013). Additionally, administration of a fibre-rich cocoa product to moderately hypercholesterolemic humans evoked a hypoglycaemic effect (Sarriá, B. et al., 2014) and consumption of cocoa powder for six weeks lowered blood cholesterol, low density lipoprotein (LDL)-cholesterol and inflammation markers in patients with T2D (Parsaeyan, N. et al., 2014). Finally, acute cocoa supplementation increased postprandial HDL-cholesterol and insulin in obese adults with T2D after consumption of a high-fat breakfast (Basu, A. et al., 2015). Nevertheless, some studies have shown no effect of a cocoa diet on T2D biomarkers. Thus, consumption of a flavanol rich cocoa drink (150 mL twice a day, approximately 900 mg of flavanols) for 2 weeks improved endothelial function in patients with hypertension without changing BP or insulin sensitivity (Muniyappa, R. et al., 2008). Moreover, in a study by Balzer and colleagues (2008), T2D patients receiving a cocoa diet with a high daily dose of 963 mg of flavanols for 30 days showed a significantly increase in fasting flow-mediated vascular dilation but BP, heart rate, and glycaemic control were unaffected. Also in this line, a short-term intake of cocoa and green tea beverages rich in flavanols does not appear to improve glucose metabolism, but they do affect selected markers of one or

more measures of oxidative stress and inflammation in obese adults at risk for insulin resistance (Stote, K.S. et al., 2012).

Regarding intervention studies with catechins, EC supplementation to healthy adults has been reported to improve fasting plasma insulin and insulin resistance (HOMA-IR) and had no effect on fasting plasma glucose. EC did not change BP, arterial stiffness, nitric oxide, endothelin 1, or blood lipid profile (Dower, J.I. et al., 2015). Based on the above studies, a combined therapy of metformin and epicatechin has been very recently suggested for T2D patients (Moreno-Ulloa, A. and Moreno-Ulloa, J., 2016).

Altogether, these studies provide evidence that regular consumption of cocoa flavanols or EC-rich foods could constitute a dietary strategy to mitigate obesity-associated insulin resistance. In fact, a most interesting finding in recent human studies including cocoa interventions is that cocoa powder did not induce any weight gain or other anthropometric changes (Martínez-López, S. et al., 2014). Hence, although cocoa products are usually high-energy foods, they have been shown to have anti-obesity effects in humans (Visioli, F. et al., 2009) and rats (Cordero-Herrera, I. et al., 2015, Farhat, G. et al., 2014, Fernández-Millán, E. et al., 2015, Gu, Y. et al., 2014, Matsui, N. et al., 2005). However, in prospective cohort studies Greenberg and coworkers (2013, 2015) have reported that habitual chocolate intake was associated with greater prospective weight gain over time in a dose-response manner, also in postmenopausal women. Indeed, the greatest weight gain was observed in participants with the highest frequency of chocolate intake, which could also be partly due to decreased satiety induced by the regular intake of chocolate. However, in a cross-sectional analysis of data from one of the studies an inverse association between chocolate intake and current BMI was detected only in participants with preexisting serious obesity-related illness (Greenberg, J.A. and Buijsse, B., 2013). This difference between the prospective and

cross-sectional findings was explained because participants with high BMI who were diagnosed with obesity-related illnesses tended to reduce their intake of energy-rich foods, including chocolate, in an attempt to improve their prognosis - and thereby caused the observed inverse cross-sectional association between chocolate intake and BMI. It should also be highlighted that in the mentioned work it was not differentiated among between different types of chocolate (white, milk, plain) (Greenberg, J.A. and Buijsse, B., 2013). On the contrary, in the second study with postmenopausal women, more chocolate-candy consumption, most likely milk chocolate, was associated with greater weight gain during our 3-year study period in the Women's Health Initiative cohort (Greenberg, J.A. et al., 2015). In this line, it should be mentioned that a dark chocolate habit seems more likely than a milk chocolate habit to be able to yield long-term cardiovascular benefits with lower risk of weight gain (Farhat, G. et al., 2014), and dark chocolate may also be able to induce stronger feelings of satiety and lead to lower energy intake than milk chocolate (Sørensen, L.B. and Astrup, A., 2011). Moreover, studies performed in cultured cells and experimental animals suggest that the positive effect of cocoa and its flavanols on T2D seems to be related both to their proved beneficial effects on vascular function and on glycaemic control by modulating key proteins of the insulin signalling pathway, inflammation and stress. The specific biochemical and molecular mechanisms have been recently reviewed (Martín, M.A. et al., 2016, Strat, K.M. et al., 2016).

Therefore, it could be suggested that daily consumption of small amounts of flavanols from cocoa or dark chocolate, within the context of a healthy diet, would constitute a natural and cheap approach to potentially prevent or contribute to the treatment of T2D with minimal toxicity and adverse side effects. However the majority of commercially available cocoa or chocolate contain little flavanols and lot of sugar and calories that

may worsen glycaemic control in T2D patients. Therefore, we must be very cautious before recommending the consumption of chocolate (even in moderate amounts) in this population, emphasizing that only ingestion of products rich in natural cocoa and chocolates containing a minimum of 70% cocoa are recommended. Nevertheless, extensive well-controlled and well-designed human epidemiological and intervention studies are needed to identify targets and optimal doses of cocoa to prevent, delay or contribute to the treatment of T2D.

5.-Conclusion

Most studies presented propose a prominent role for tea, red wine and cocoa and their flavanols in the protection against diabetes as they could be considered as a potential chemopreventive tool useful for the nutritional management of this disorder. Additionally, in a number of the studies above reported one or more intrinsic mechanisms of action have been proposed, indicating a specific role for dietary flavanols in the regulation of pathophysiologic features of diabetes. Indeed, The European Food Safety Authority (EFSA) endorses that cocoa flavanols help maintain normal blood pressure (European Food Safety Authority, 2010) and endothelium-dependent vasodilation (European Food Safety Authority, 2012), and, in order to obtain the claimed effect, 200 mg of cocoa flavanols should be consumed daily. This amount of flavanols can be acquired with the intake of 100 g of most cocoa soluble products or 40 g of any 70% cocoa chocolate in the market. However, as repeatedly stated above, further intervention studies, especially those considering long-term habitual consumption with cocoa/chocolate, red wine or tea are still necessary. In addition, different confounders such as different chemical composition of teas, red wines or cocoas due to the cultivars, food processing, fermentation degree for tea leaves or

cocoa, as well as an agreement in defining high, habitual or low consumption should also be considered. All this would contribute to clarify conflicting findings and to confirm or refute the anti-diabetic effects of dietary flavanols.

Conflict of interest

The authors declare that there are no conflicts of interest.

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References

- Actis-Goretta, L., Leveques, A., Rein, M., Teml, A., Schafer, C., Hofmann, U., Li, H., Schwab, M., Eichelbaum, M. and Williamson, G., 2013. Intestinal absorption, metabolism, and excretion of (–)-epicatechin in healthy humans assessed by using an intestinal perfusion technique. *Am. J. Clin. Nutr.* 98, 924-933.
- Almoosawi, S., Tsang, C., Ostertag, L.M., Fyfed, L. and Al-Dujaili, E.A.S., 2012. Differential effect of polyphenol-rich dark chocolate on biomarkers of glucose metabolism and cardiovascular risk factors in healthy, overweight and obese subjects: a randomized clinical trial. *Food & Function*. 3, 1035-1043.
- Aron, P.M. and Kennedy, J.A., 2008. Flavan-3-ols: Nature, occurrence and biological activity. *Mol. Nutr. Food Res.* 52, 79-104.
- Artero, A., Artero, A., Tarín, J.J. and Cano, A., 2015. The impact of moderate wine consumption on health. *Maturitas*. 80, 3-13.
- Baba, S., Osakabe, N., Yasuda, A., Natsume, M., Takizawa, T., Nakamura, T. and Terao, J., 2000. Bioavailability of (2)-epicatechin upon intake of chocolate and cocoa in human volunteers. *Free Radic. Res.* 33, 635-641.
- Babu, P.V.A., Liu, D. and Gilbert, E.R., 2013. Recent advances in understanding the anti-diabetic actions of dietary flavonoids. *J. Nutr. Biochem.* 24, 1777-1789.
- Balentine, D.A., Wiseman, S.A. and Bouwens, L.C., 1997. The chemistry of tea flavonoids. *Crit. Rev. Food Sci. Nutr.* 37, 693-704.
- Balzer, J., Rassaf, T., Heiss, C., Kleinbongard, P., Lauer, T., Merx, M., Heussen, N., Gross, H.B., Keen, C.L., Schroeter, H. and Kelm, M., 2008. Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients a double-masked, randomized, controlled trial. *J. Am. Coll. Cardiol.* 51, 2141–2149.

- Bantle, A.E., Thomas, W. and Bantle, J.P., 2008. Metabolic effects of alcohol in the form of wine in persons with type 2 diabetes mellitus. *Metab. Clin. Exp.* 57, 241-245.
- Bashan, N., Kovsan, J., Kachko, I., Ovadia, H. and Rudich, A., 2009. Positive and negative regulation of insulin signaling by reactive oxygen and nitrogen species. *Physiol. Rev.* 89, 27-71.
- Basu, A., Betts, N.M., Leyva, M.J., Fu, D., Aston, C.E. and Lyons, T.J., 2015. Acute cocoa supplementation increases postprandial HDL cholesterol and insulin in obese adults with type 2 diabetes after consumption of a high-fat breakfast. *J. Nutr.* 145, 2325-2332.
- Beulens, J.W., van der Schouw, Y.T., Bergmann, M.M., Rohrmann, S., Schulze, M.B., Buijsse, B., Grobbee, D.E., Arriola, L., Cauchi, S., Tormo, M.J., Allen, N.E., van der A, D.L., Balkau, B., Boeing, H., Clavel-Chapelon, F., de Lauzon-Guillan, B., Franks, P., Froguel, P., Gonzales, C., Halkjaer, J., Huerta, J.M., Kaaks, R., Key, T.J., Khaw, K.T., Krogh, V., Molina-Montes, E., Nilsson, P., Overvad, K., Palli, D., Panico, S., Ramón-Quirós, J., Rolandsson, O., Romieu, I., Romaguera, D., Sacerdote, C., Sánchez, M.J., Spijkerman, A.M., Teucher, B., Tjonneland, A., Tumino, R., Sharp, S., Forouhi, N.G., Langenberg, C., Feskens, E.J., Riboli, E., Wareham, N.J. and InterAct-Consortium, 2012. Alcohol consumption and risk of type 2 diabetes in European men and women: influence of beverage type and body size. The EPIC-InterAct study. *J. Intern. Med.* 272, 358-370.
- Bhupathiraju, S.N., Pan, A., Malik, V.S., Manson, J.E., Willett, W.C., van Dam, R.M. and Hu, F.B., 2013. Caffeinated and caffeine-free beverages and risk of type 2 diabetes. *Am. J. Clin. Nutr.* 97, 163-174.
- Blomster, J.I., Zoungas, S., Chalmers, J., Li, Q., Chow, C.K., Woodward, M., Mancia, G., Poulter, N., Williams, B., Harrap, S., Neal, B., Patel, A. and Hillis, G.S., 2014. The

relationship between alcohol consumption and vascular complications and mortality in individuals with type 2 diabetes. *Diabetes Care* 37, 1353-1359.

Borges, C.M., Papadimitriou, A., Duarte, D.A., Lopes de Faria, J.M. and Lopes de Faria, J.B., 2016. The use of green tea polyphenols for treating residual albuminuria in diabetic nephropathy: A double-blind randomised clinical trial. *Sci. Rep.* 6, 28282.

Buitrago-Lopez, A., Sanderson, J., Johnson, L., Warnakula, S., Wood, A., Di Angelantonio, E. and Franco, O.H., 2011. Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis. *Brit. Med. J.* 343, 4488-4495.

Cordero-Herrera, I., Martín, M.A., Escrivá, F., Álvarez, C., Goya, L. and Ramos, S., 2015. Cocoa-rich diet ameliorates hepatic insulin resistance by modulating insulin signaling and glucose homeostasis in Zucker diabetic fatty rats. *J. Nutr. Biochem.* 26, 704-712.

Crichton, G.E., Elias, M.F., Dearborn, P. and Robbins, M., 2017. Habitual chocolate intake and type 2 diabetes mellitus in the Maine-Syracuse Longitudinal Study: (1975-2010): Prospective observations. *Appetite.* 108, 263-269.

Cullmann, M., Hilding, A. and Östenson, C.G., 2012. Alcohol consumption and risk of prediabetes and type 2 diabetes development in a Swedish population. *Diabet. Med.* 29, 441-452.

Curtis, P.J., Potter, J., Kroon, P.A., Wilson, P., Dhatariya, K., Sampson, M. and Cassidy, A., 2013. Vascular function and atherosclerosis progression after 1 year of flavonoid intake in statin-treated postmenopausal women with type 2 diabetes: a double-blind randomized controlled trial. *Am. J. Clin. Nutr.* 97, 936-942.

Curtis, P.J., Sampson, M., Potter, J., Dhatariya, K., Kroon, P.A. and Cassidy, A., 2012. Chronic ingestion of flavan-3-ols and isoflavones improves insulin sensitivity and lipoprotein status and attenuates estimated 10-Year CVD risk in medicated postmenopausal women with type 2 diabetes. *Diabetes Care* 35, 226-232.

- Chaturvedi, N., 2007. The burden of diabetes and its complications: trends and implications for intervention. *Diabetes Res. Clin. Pract.* 76, S3-S12.
- Chaturvedula, V.S.P. and Prakash, I., 2011. The aroma, taste, color and bioactive constituents of tea. *J. Med. Plants Res.* 5, 2110-2114.
- Chiva-Blanch, G., Urpi-Sarda, M., Ros, E., Valderas-Martinez, P., Casas, R., Arranz, S., Guillén, M., Lamuela-Raventós, R.M., Llorach, R., Andres-Lacueva, C. and Estruch, R., 2013. Effects of red wine polyphenols and alcohol on glucose metabolism and the lipid profile: A randomized clinical trial. *Clin. Nutr.* 32, 200-206.
- Davison, K., Coates, A.M., Buckley, J.D. and Howe, P.R.C., 2008. Effect of cocoa flavanols and exercise on cardiometabolic risk factors in overweight and obese subjects. *Int. J. Obes. (London)*. 32, 1289-1296.
- Del Rio, D., Rodriguez-Mateos, A., Spencer, J.P.E., Tognolini, M., Borges, G. and Crozier, A., 2013. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid. Redox Signal.* 18, 1818-1892.
- Dembinska-Kiec, A., Mykkänen, O., Kiec-Wilk, B. and Mykkänen, H., 2008. Antioxidant phytochemicals against type 2 diabetes. *Br. J. Nutr.* 99, ES109-ES117.
- Dower, J.I., Geleijnse, J.M., Gijbbers, L., Zock, P.L., Kromhout, D. and Hollman, P.C.H., 2015. Effects of the pure flavonoids epicatechin and quercetin on vascular function and cardiometabolic health: a randomized, double-blind, placebo-controlled, crossover trial. *Am. J. Clin. Nutr.* 101, 914-921.
- Ellam, S. and Williamson, G., 2013. Cocoa and human health. *Annu. Rev. Nutr.* 33, 105-128.
- European Food Safety Authority, 2010. Scientific Opinion on the substantiation of health claims related to cocoa flavanols and protection of lipids from oxidative damage and maintenance of normal blood pressure. *EFSA J.* 8, 1792.

- European Food Safety Authority, 2012. Scientific opinion on the substantiation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation. *EFSA J.* 10, 2809.
- Fagherazzi, G., Vilier, A., Lajous, M., Boutron-Ruault, M.-C., Balkau, B., Clavel-Chapelon, F. and Bonnet, F., 2014. Wine consumption throughout life is inversely associated with type 2 diabetes risk, but only in overweight individuals: results from a large female French cohort study. *Eur. J. Epidemiol.* 29, 831-839.
- Farhat, G., Drummond, S., Fyfe, L. and Al-Dujaili, E.A., 2014. Dark chocolate: an obesity paradox or a culprit for weight gain? *Phytother. Res.* 28, 791-797.
- Fernandes, I., Pérez-Gregorio, R., Soares, S., Mateus, N. and de Freitas, V., 2017. Wine flavonoids in health and disease prevention. *Molecules.* 22, 292; doi:10.3390.
- Fernández-Millán, E., Cordero-Herrera, I., Ramos, S., Escrivá, F., Álvarez, C., Goya, L. and Martín, M.A., 2015. Cocoa-rich diet attenuates beta cell mass loss and function in young Zucker diabetic fatty rats by preventing oxidative stress and beta cell apoptosis. *Mol. Nutr. Food Res.* 59, 820-824.
- Fukino, Y., Shimbo, M., Aoki, N., Okubo, T. and Iso, H., 2005. Randomized controlled trial for an effect of green tea consumption on insulin resistance and inflammation markers. *J. Nutr. Sci. Vitaminol. (Tokyo).* 51, 335-342.
- Gepner, Y., Golan, R., Harman-Boehm, I., Henkin, Y., Schwarzfuchs, D., Shelef, I., Durst, R., Kovsan, J., Bolotin, A., Leitersdorf, E., Shpitzen, S., Balag, S., Shemesh, E., Witkow, S., Tangi-Rosental, O., Chassidim, Y., Liberty, I.F., Sarusi, B., Ben-Avraham, S., Helander, A., Ceglarek, U., Stumvoll, M., Blüher, M., Thiery, J., Rudich, A., Stampfer, M.J. and Shai, I., 2015. Effects of initiating moderate alcohol intake on cardiometabolic risk in adults with type 2 diabetes: A 2-year randomized, controlled trial. *Ann. Intern. Med.* 163, 569-579.

- Golan, R., Shelef, I., Shemesh, E., Henkin, Y., Schwarzfuchs, D., Gepner, Y., Harman-Boehm, I., Witkow, S., Friger, M., Chassidim, Y., Liberty, I.F., Sarusi, B., Serfaty, D., Bril, N., Rein, M., Cohen, N., Ben-Avraham, S., Ceglarek, U., Stumvoll, M., Blüher, M., Thiery, J., Stampfer, M.J., Rudich, A. and Shai, I., Effects of initiating moderate wine intake on abdominal adipose tissue in adults with type 2 diabetes: a 2-year randomized controlled trial. *Public Health Nutr.* 20, 549-555.
- Grassi, D., Desideri, G. and Ferri, C., 2013. Protective effects of dark chocolate on endothelial function and diabetes. *Curr. Opin. Clin. Nutr. Metab. Care.* 16, 662-668.
- Grassi, D., Desideri, G., Mai, F., Martella, L., De Feo, M., Soddu, D., Fellini, E., Veneri, M., Stamerra, C.A. and Ferri, C., 2015. Cocoa, glucose tolerance, and insulin signaling: Cardiometabolic protection. *J. Agric. Food Chem.* 63, 9919–9926.
- Grassi, D., Desideri, G., Necozione, S., Lippi, C., Casale, R., Properzi, G., Blumberg, J.B. and Ferri, C., 2008. Blood pressure is reduced and insulin sensitivity increased in glucose-intolerant, hypertensive subjects after 15 days of consuming high-polyphenol dark chocolate. *J. Nutr.* 138, 1671-1676.
- Grassi, D., Lippi, C., Necozione, S., Desideri, G. and Ferri, C., 2005a. Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons. *Am. J. Clin. Nutr.* 81, 611-614.
- Grassi, D., Necozione, S., Lippi, C., Croce, G., Valeri, L., Pasqualetti, P., Desideri, G., Blumberg, J.B. and Ferri, C., 2005b. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. *Hypertension.* 46, 398-405.
- Greenberg, J.A., 2015. Chocolate-candy consumption and three-year weight gain among postmenopausal American women. *Obesity.* 23, 677-683.

- Greenberg, J.A., Axen, K.V., Schnoll, R. and Boozer, C.N., 2005. Coffee, tea and diabetes: the role of weight loss and caffeine. *Int. J. Obes.* 29, 1121-1129.
- Greenberg, J.A. and Buijsse, B., 2013. Habitual chocolate consumption may increase body weight in a dose-response manner. *PLoS One.* 8, e70271.
- Greenberg, J.A., Manson, J.E., Buijsse, B., Wang, L., Allison, M.A., Neuhouser, M.L., Tinker, L., Waring, M.E., Isasi, C.R., Martin, L.W. and Thomson, C.A., 2015. Chocolate-candy consumption and three-year weight gain among postmenopausal American women. *Obesity.* 23, 677-683.
- Greenberg, J.A., Manson, J.E., Tinker, L., Neuhouser, M.L., Garcia, L., Vitolins, M.Z. and Phillips, L.S., 2017. Chocolate intake and diabetes risk in postmenopausal American women. *Eur. J. Clin. Nutr.* doi:10.1038/ejcn.2017.36.
- Gu, Y., Yu, S. and Lambert, J.D., 2014. Dietary cocoa ameliorates obesity-related inflammation in high fat-fed mice. *Eur. J. Nutr.* 53, 149-158.
- Guillausseau, P.J., Meas, T., Virally, M., Laloi-Michelin, M., Médeau, V. and Kevorkian, J.P., 2008. Abnormalities in insulin secretion in type 2 diabetes mellitus. *Diabetes Metab. Res. Rev.* 34, S43-S48.
- Hamer, M., Witte, D.R., Mosdøl, A., Marmot, M.G. and Brunner, E.J., 2008. Prospective study of coffee and tea consumption in relation to risk of type 2 diabetes mellitus among men and women: The Whitehall II study. *Br. J. Nutr.* 100, 1046-1053.
- Hayashino, Y., Fukuhara, S., Okamura, T., Tanaka, T. and Ueshima, H.f.t.H.-O.R.G., 2011. High oolong tea consumption predicts future risk of diabetes among Japanese male workers: a prospective cohort study. *Diabet. Med.* 28, 805-810.
- He, Z.X., Zhou, Z.W., Yang, Y., Yang, T., Pan, S.Y., Qiu, J.X. and Zhou, S.F., 2015. Overview of clinically approved oral antidiabetic agents for the treatment of type 2 diabetes mellitus. *Clin. Exp. Pharmacol. Physiol.* 42, 125-138.

- Hodge, A.M., English, D.R., O'Dea, K. and Giles, G.G., 2006. Alcohol intake, consumption pattern and beverage type, and the risk of type 2 diabetes. *Diabet. Med.* 23, 690-697.
- Holt, R.R., Lazarus, S.A., Sullards, M.C., Zhu, Q.Y., Schramm, D.D., Hammerstone, J.F., Fraga, C.G., Schmitz, H.H. and Keen, C.L., 2002. Procyanidin dimer B2 [epicatechin-(4b-8)-epicatechin] in human plasma after the consumption of a flavanol-rich cocoa. *Am. J. Clin. Nutr.* 76, 798-804.
- Hooper, L., Kay, C., Abdelhamid, A., Kroon, P.A., Cohn, J.S., Rimm, E.B. and Cassidy, A., 2012. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. *Am. J. Clin. Nutr.* 95, 740-751.
- Hosoda, K., Wang, M.-F., Liao, M.-L., Chuang, C.-K., Iha, M., Clevidence, B. and Yamamoto, S., 2003. Antihyperglycemic effect of oolong tea in type 2 diabetes. *Diabetes Care.* 26, 1714-1718.
- Hsu, C.H., Liao, Y.L., Lin, S.C., Tsai, T.H., Huang, C.J. and Chou, P., 2011. Does supplementation with green tea extract improve insulin resistance in obese type 2 diabetics? A randomized, double-blind, and placebo-controlled clinical trial. *Altern. Med. Rev.* 16, 157-163.
- Huang, J., Wang, X. and Zhang, Y., 2016. Specific types of alcoholic beverage consumption and risk of type 2 diabetes: a systematic review and meta-analysis. *J. Diabetes Invest.* 8, 56-68.
- Huxley, R., Lee, C.M.Y., Barzi, F., Timmermeister, L., Czernichow, S., Perkovic, V., Grobbee, D.E., Batty, D. and Woodward, M., 2009. Coffee, decaffeinated coffee, and tea consumption in relation to incident type 2 diabetes mellitus. *Arch. Intern. Med.* 169, 2053-2063.

- Iso, H., Date, C., Wakai, K., Fukui, M., Tamakoshi, A. and Group, J.S., 2006. The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. *Ann. Intern. Med.* 2006, 554-562.
- Jing, Y., Han, G., Hu, Y., Bi, Y., Li, L. and Zhu, D., 2009. Tea onsumption and risk of type 2 diabetes: a meta-analysis of cohort studies. *J. Gen. Intern. Med.* 24, 557-562.
- Kim, J., Kim, J., Shim, S., Lee, C.-Y., Lee, K.-W. and Lee, H.-J., 2014. Cocoa phytochemicals: recent advances in molecular mechanisms on health. *Crit. Rev. Food Sci. Nutr.* 54, 1458-1472.
- Kolka, C.M. and Bergman, R.N., 2013. The endothelium in diabetes: Its role in insulin access and diabetic complications. *Rev. Endocr. Metab. Disord.* 14, 13-19.
- Lee, K.W., Kim, Y.J., Lee, H.J. and Lee, C.Y., 2003. Cocoa has more phenolic phytochemicals and a higher antioxidant capacity than teas and red wine. *J. Agric. Food Chem.* 51, 7292–7295.
- Lin, X., Zhang, I., Li, A., Manson, J.E., Sesso, H.D., Wang, L. and Liu, S., 2016. Cocoa flavanol intake and biomarkers for cardiometabolic health: A systematic review and meta-analysis of randomized controlled trials. *J. Nutr.* 146, 2325-2333.
- Liu, C.-Y., Huang, C.-J., Huang, L.-H., Chen, I.-J., Chiu, J.-P.-. and Hsu, C.-H., 2014. Effects of green tea extract on insulin resistance and glucagon-like peptide 1 in patients with type 2 diabetes and lipid abnormalities: A randomized, double-blinded, and placebo-controlled trial. *PloS One.* 9, e91163.
- Ma, Q., Chen, D., Sun, H.-P., Yan, N., Y, X. and Pan, C.-W., 2015. Regular chinese green tea consumption is protective for diabetic retinopathy: a clinic-based case-control study. *J. Diabetes Res.* [dx.doi.org/10.1155/2015/231570](https://doi.org/10.1155/2015/231570)

- MacKenzie, T., Leary, L. and Brooks, W.B., 2007. The effect of an extract of green and black tea on glucose control in adults with type 2 diabetes mellitus: double-blind randomized study. *Metab. Clin. Exp.* 56, 1340-1344.
- Mahmoud, F., Haines, D., Al-Ozairi, E. and Dashti, A., 2016. Effect of black tea consumption on intracellular cytokines, regulatory T cells and metabolic biomarkers in type 2 diabetes patients. *Phytother. Res.* 30, 454-462.
- Manach, C., Scalbert, A., Morand, C., Remesy, C. and Jimenez, L., 2004. Polyphenols: food sources and bioavailability. *Am J Clin Nutr.* 79, 727-747.
- Manach, C., Williamson, G., Morand, C., Scalbert, A. and Rémésy, C., 2005. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am. J. Clin. Nutr.* 81(suppl), 230S-242S.
- Marchetti, P., Bugliani, M., Boggi, U., Masini, M. and Marselli, L., 2012. The pancreatic beta cells in human type 2 diabetes. *Adv. Exp. Med. Biol.* 771, 288-309.
- Marfella, R., Cacciapuoti, F., Siniscalchi, M., Sasso, F.C., Marchese, F., Cinone, F., Musacchio, E., Marfella, M.A., Ruggiero, L., Chiorazzo, G., Liberti, D., Chiorazzo, G., Nicoletti, G.F., Saron, C., D'Andrea, F., Ammendola, C., Verza, M. and Coppola, L., 2006. Effect of moderate red wine intake on cardiac prognosis after recent acute myocardial infarction of subjects with type 2 diabetes mellitus. *Diabetic Med.* 23, 974-981.
- Marques-Vidal, P., Vollenweider, P. and Waeber, G., 2015. Alcohol consumption and incidence of type 2 diabetes. Results from the CoLaus study. *Nutr. Metab. Cardio. Dis.* 25, 75-84.
- Martín, M.A., Goya, L. and Ramos, S., 2016. Antidiabetic actions of cocoa flavanols. *Mol. Nutr. Food Res.* 60, 1756-1769.

- Martínez-López, S., Sarriá, B., Sierra-Cinos, J.L., Goya, L., Mateos, R. and L, B., 2014. Realistic intake of a flavanol-rich soluble cocoa product increases HDL-cholesterol without inducing anthropometric changes in healthy and moderately hypercholesterolemic subjects. *Food & Function*. 5, 364-374.
- Matsui, N., Ito, R., Nishimura, E., Yoshikawa, M., Kato, M., Kamei, M., Shibata, H., Matsumoto, I., Abe, K. and Hashizume, S., 2005. Ingested cocoa can prevent high-fat diet-induced obesity by regulating the expression of genes for fatty acid metabolism. *Nutrition*. 21, 594-601.
- Matsumoto, C., Petrone, A.B., Sesso, H.D., Gaziano, J.M. and Djouss, L., 2015. Chocolate consumption and risk of diabetes mellitus in the Physicians' Health Study. *Am. J. Clin. Nutr.* 101, 362-367.
- Mellor, D.D., Sathyapalan, T., Kilpatrick, E.S. and Atkin, S.L., 2015. Diabetes and chocolate: friend or foe? *J. Agric. Food Chem.* 63, 9910-9918.
- Mellor, D.D., Sathyapalan, T., Kilpatrick, E.S., Beckett, S. and Atkin, S.L., 2010. High-cocoa polyphenol-rich chocolate improves HDL cholesterol in Type 2 diabetes patients. *Diabet. Med.* 27, 1318-1321.
- Mirzaei, K., Hossein-Nezhad, A., Karimi, M., Hosseinzadeh-Attar, M.J., Jafari, N., Najmafshar, A. and Larijani, B., 2009. Effect of green tea extract on bone turnover markers in type 2 diabetic patients; A double- blind, placebo-controlled clinical trial study. *DARU*. 17, 39-45.
- Moreno-Ulloa, A. and Moreno-Ulloa, J., 2016. Mortality reduction among persons with type 2 diabetes: Epicatechin as add-on therapy to metformin? . *Med. Hypotheses*. 91, 86-89.
- Mousavi, A., Vafa, M., Neyestani, T., Khamseh, M. and Hoseini, F., 2013. The effects of green tea consumption on metabolic and anthropometric indices in patients with type 2 diabetes. *J. Res. Med. Sci.* 18, 1080–1086.

- Mozaffari-Khosravi, H., Ahadi, Z. and K, B., 2013. The effect of green tea and sour tea on blood pressure of patients with type 2 diabetes: a randomized clinical trial. *J. Diet Suppl.* 10, 105-115.
- Muniyappa, R., Hall, G., Kolodziej, T.L., Karne, R.J., Crandon, S.K. and Quon, M.J., 2008. Cocoa consumption for 2 wk enhances insulin-mediated vasodilatation without improving blood pressure or insulin resistance in essential hypertension. *Am. J. Clin. Nutr.* 88, 1685-1696.
- Nagao, T., Meguro, S., Hase, T., Otsuka, K., Komikado, M., Tokimitsu, I., Yamamoto, T. and Yamamoto, K., 2009. A catechin-rich beverage improves obesity and blood glucose control in patients with type 2 diabetes. *Obesity.* 17, 310-317.
- Napoli, R., Cozzolino, D., Guardasole, V., Angelini, V., Zarra, E., Matarazzo, M., Cittadini, A., Saccà, L. and Torel, I.R., 2005. Red wine consumption improves insulin resistance but not endothelial function in type 2 diabetic patients. *Metab. Clin. Exp.* 54, 306-313.
- Neyestani, T.R., Nastaran, S., Kalayi, A., Gharavi, A., Khalaji, N., Dadkhah, M., Zowghi, T., Haidari, H. and Shab-bidar, S., 2010. Regular daily intake of black tea improves oxidative stress biomarkers and decreases serum C-reactive protein levels in type 2 diabetic ptients. *Ann. Nutr. Metab.* 57, 40-49.
- Oba, S., Nagata, C., Nakamura, K., Fujii, K., Kawachi, T., Takatsuka, N. and Shimizu, H., 2010. Consumption of coffee, green tea, oolong tea, black tea, chocolate snacks and the caffeine content in relation to risk of diabetes in Japanese men and women. *Br. J. Nutr.* 103, 453-459.
- Odegaard, A.O., Pereira, M.A., ., Koh, W.-P., Arakawa, K., Lee, H.-P. and Yu, M.C., 2008. Coffee, tea, and incident type 2 diabetes: the Singapore Chinese Health Study. *Am. J. Clin. Nutr.* 88, 979-985.

- Parsaeyan, N., Mozaffari-Khosravi, H., Absalan, A. and Mozayan, M.R., 2014. Beneficial effects of cocoa on lipid peroxidation and inflammatory markers in type 2 diabetic patients and investigation of probable interactions of cocoa active ingredients with prostaglandin synthase-2 (PTGS-2/COX-2) using virtual analysis. *J. Diabetes Metab. Disord.* 13, 30-38.
- Pastoriza, S., Mesías, M., Cabrera, C. and Rufián-Henares, J.A., 2017. Healthy properties of green and white teas: an update. *Food & Function*. doi: 10.1039/c7fo00611j
- Poitout, V. and Robertson, R.P., 2008. Glucolipotoxicity: fuel excess and beta-cell dysfunction. *Endocr Rev.* 29, 351-366.
- Polychronopoulos, E., Zeimbekis, A., Kastorini, C.-M., Papairakleous, N., Vlachou, I., Bountziouka, V. and Panagiotakos, D.B., 2008. Effects of black and green tea consumption on blood glucose levels in non-obese elderly men and women from Mediterranean Islands (MEDIS epidemiological study). *Eur. J. Nutr.* 47, 10-16.
- Ramírez-Sánchez, I., Taub, P.R., Ciaraldi, T.P., Nogueira, L., Coe, T., Perkins, G., Hogan, M., Maisel, A.S., Henry, R.R., Ceballos, G. and Villarreal, F., 2013. (-)-Epicatechin rich cocoa mediated modulation of oxidative stress regulators in skeletal muscle of heart failure and type 2 diabetes patients. *Int. J. Cardiol.* 168, 3982-3990.
- Ramos, S., 2008. Cancer chemoprevention and chemotherapy: dietary polyphenols and signalling pathways. *Mol. Nutr. Food Res.* 52, 507-526.
- Rasmussen, S.E., Frederiksen, H., Struntze-Krogholm, K. and Poulsen, L., 2005. Dietary proanthocyanidins: occurrence, dietary intake, bioavailability, and protection against cardiovascular disease. *Mol. Nutr. Food Res* 49, 159-174.
- Rasouli, B., Ahlbom, A., Andersson, T., Grill, V., Midthjell, K., Olsson, L. and Carlsson, S., 2013. Alcohol consumption is associated with reduced risk of type 2 diabetes and

- autoimmune diabetes in adults: results from the Nord-Trøndelag Health Study. *Diabet. Med* 30, 56-64.
- Robertson, R.P., 2004. Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic islet beta cells in diabetes. *J. Biol. Chem.* 279, 42351-42354.
- Robertson, R.P., 2010. Antioxidant drugs for treating beta-cell oxidative stress in type 2 diabetes: glucose-centric versus insulin-centric. *Therapy Discov. Med.* 9, 132-137.
- Robertson, R.P., 2014. Red wine and diabetes health: Getting skin in the ame. *Diabetes.* 63, 31-38.
- Robinson, L.E., Savani, S., Battram, D.S., McLaren, D.H., Sathasivam, P. and Graham, T.E., 2004. Caffeine ingestion before an oral glucose tolerance test impairs blood glucose management in men with type 2 diabetes. *J. Nutr.* 134, 2528-2533.
- Rostami, A., Khalili, M., Haghighat, N., Egtesad, S., Shidfar, F., Heidari, I. Ebrahimpour-Koujan, S. and Egtesadi, M., 2015. High-cocoa polyphenol-rich chocolate improves blood pressure in patients with diabetes and hypertension. *ARYA Atheroscler.* 11, 21-29.
- Roura, E., Andres-Lacueva, C., Jauregui, O., Badia, E., Estruch, R., Izquierdo-Pulido, M. and Lamuela-Raventós, R.M., 2005. Rapid liquid chromatography tandem mass spectrometry assay to quantify plasma (2)-epicatechin metabolites after ingestion of a standard portion of cocoa beverage in humans. *J. Agric. Food Chem.* 53, 6190-6194.
- Rusconi, M. and Conti, A., 2010. *Theobroma cacao* L., the food of the Gods: A scientific approach beyond myths and claims. *Pharmacol. Res.* 61, 5-13.
- Ryu, O.H., Lee, J., Lee, K.W., Kim, H.Y., Seo, J.A., Kim, S.G., Kim, N.H., Baik, S.H., Choi, D.S. and Choi, K.M., 2006. Effects of green tea consumption on inflammation, insulin resistance and pulse wave velocity in type 2 diabetes patients. *Diabetes Res. Clin. Pract.* 71, 356-358.

- Sarriá, B., Martínez-López, S., Sierra-Cinos, J.L., García-Diz, L., Mateos, R. and Bravo-Clemente, L., 2014. Regular consumption of a cocoa product improves the cardiometabolic profile in healthy and moderately hypercholesterolaemic adults. *Brit. J. Nutr.* 111, 122-134.
- Serra, A., Macia, A., Romero, M.P., Valls, J., Blade, C., Arola, L. and Motilva, M.J., 2010. Bioavailability of procyanidin dimers and trimers and matrix food effects in in vitro and in vivo models. *Br. J. Nutr.* 103, 944-952.
- Shai, I., Wainstein, J., Harman-Boehm, I., Raz, I., Fraser, D., Rudich, A. and Stampfer, M.J., 2007. Glycemic effects of moderate alcohol intake among patients with type 2 diabetes. *Diabetes Care.* 30, 3011-3016.
- Shrime, M.G., Bauer, S.R., McDonald, A.C., Chowdhury, N.H., Coltart, C.E. and Ding, E.L., 2011. Flavonoid-rich cocoa consumption affects multiple cardiovascular risk factors in a meta-analysis of short-term studies. *J. Nutr.* 141, 1982-1988.
- Song, Y., Manson, J.A.E., Buring, J.E., Sesso, H.D. and Liu, S., 2005. Associations of dietary flavonoids with risk of type 2 diabetes, and markers of insulin resistance and systemic inflammation in women: a prospective study and cross-sectional analysis. *J. Am. Coll. Nutr.* 24, 376-384.
- Sørensen, L.B. and Astrup, A., 2011. Eating dark and milk chocolate: A randomized crossover study of effects on appetite and energy intake. *Nutr Diabetes.* 1, e21. doi:10.1038.
- Spencer, J.P.E., 2003. Metabolism of tea flavonoids in the gastrointestinal tract. *J. Nutr.* 133, 3255S-3261S.
- Stockley, C., Teissedre, P.-L., Boban, M., Di Lorenzo, C. and Restani, P., 2012. Bioavailability of wine-derived phenolic compounds in humans: a review. *Food & Function.* 3, 995-1007.

- Stote, K.S., Clevidence, B.A., Novotny, J.A., Henderson, T., Radecki, S.V. and Baer, D.J., 2012. Effect of cocoa and green tea on biomarkers of glucose regulation, oxidative stress, inflammation and hemostasis in obese adults at risk for insulin resistance. *Eur. J. Clin. Nutr.* 66, 1153-1159.
- Strat, K.M., Rowley, T.J.t., Smithson, A.T., Tessem, J.S., Hulver, M.W., Liu, D., Davy, B.M., Davy, K.P. and Neilson, A.P., 2016. Mechanisms by which cocoa flavanols improve metabolic syndrome and related disorders. *J. Nutr. Biochem.* 35, 1-21.
- Tabernero, M., Serrano, J. and Saura-Calixto, F., 2006. The antioxidant capacity of cocoa products: contribution to the Spanish diet. *Int. J. Food Sci. Tech.* 41, 28-32.
- Tousoulis, D., Papageorgiou, N., Androulakis, E., Siasos, G., Latsios, G., Tentolouris, K. and Stefanadis, C., 2013. Diabetes mellitus-associated vascular impairment. Novel circulating biomarkers and therapeutic approaches. *J. Am. Coll. Cardiol.* 62, 667-676.
- Tsang, C., Auger, C., Mullen, W., Borner, A., Rouanet, J.M., Crozier, A. and Teissedre, P.L., 2005. The absorption, metabolism and excretion of flavan-3-ols and procyanidins following the ingestion of a grape seed extract by rats. *Br. J. Nutr.* 94, 170-181.
- Urpi-Sarda, M., Monagas, M., Khan, N., Lamuela-Raventos, R.M., Santos-Buelga, C., Sacanella, E., Castell, M., Permanyer, J. and Andres-Lacueva, C., 2009. Epicatechin, procyanidins, and phenolic microbial metabolites after cocoa intake in humans and rats. *Anal. Bioanal. Chem.* 394, 1545-1556.
- van Dieren, S., Uiterwaal, C.S.P.M., van der Schouw, Y.T., van der A, D.L., Boer, J.M.A., Spijkerman, A., Grobbee, D.E. and Beulens, J.W.J., 2009. Coffee and tea consumption and risk of type 2 diabetes. *Diabetologia.* 52, 2561-2569.
- Versari, D., Daghini, E., Virdis, A., Ghiadoni, L. and Taddei, S., 2009. Endothelial dysfunction as a target for prevention of cardiovascular disease. *Diabetes Care.* 32, S314-S321.

- Visioli, F., Bernaert, H., Corti, R., Ferri, C., Heptinstall, S., Molinari, E., Poli, A., Serafini, M., Smit, H.J., Vinson, J.A., Violi, F. and Paoletti, R., 2009. Chocolate, lifestyle, and health. *Crit. Rev. Food Sci. Nutr.* 49, 299-312.
- Vitale, M., Masulli, M., Rivellesse, A.A., Bonora, E., Cappellini, F., Nicolucci, A., Squatrito, S., Antenucci, D., Barrea, A., Bianchi, C., Bianchini, F., Fontana, L., Fornengo, P., Giorgino, F., Gnasso, A., Mannucci, E., Mazzotti, A., Nappo, R., Palena, A.P., Pata, P., Perriello, G., Potenziani, S., Radin, R., Ricci, L., Romeo, F., Santini, C., Scarponi, M., Serra, R., Timi, A., Turco, A.A., Vedovato, M., Zavaroni, D., Grioni, S., Riccardi, G., Vaccaro, O. and Group., T.I.S., 2016. Dietary intake and major food sources of polyphenols in people with type 2 diabetes: The TOSCA.IT Study. *Eur. J. Nutr.* DOI 10.1007/s00394-016-1355-1.
- Wei, W., Liu, Q., Tan, Y., Liu, L., Li, X. and Cai, L., 2009. Oxidative stress, diabetes, and diabetic complications. *Hemoglobin.* 33, 370-377.
- Whiting, D.R., Guariguata, L., Weil, C. and Shaw, J., 2011. IDF Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res. Clin. Pract.* 94, 311-321.
- Yang, J., Q.-X., M., H.-X., X., Ma, X. and Zeng, C.-Y., 2014. Tea consumption and risk of type 2 diabetes mellitus: a systematic review and meta-analysis update. *BMJ Open.* 4, e005632.
- Yang, W.-S., Wang, W.-Y., Fan, W.-Y., Deng, Q. and Wang, X., 2014. Tea consumption and risk of type 2 diabetes: a dose-response meta-analysis of cohort studies. *Br. J. Nutr.* 111, 1329-1339.
- Yuan, S., Li, X., Jin, Y. and Lu, J., 2017. Chocolate consumption and risk of coronary heart disease, stroke, and diabetes: A meta-analysis of prospective studies. *Nutrients.* 9, doi: 10.3390/nu9070688.

Zamora-Ros, R., Forouhi, N.G., Sharp, S.J., González, C.A., Buijsse, B., Guevara, M., van der Schouw, Y.T., Amiano, P., Boeing, H., Bredsdorff, L., Fagherazzi, G., Feskens, E.J., Franks, P.W., Grioni, S., Katzke, V., Key, T.J., Khaw, K.T., Kühn, T., Masala, G., Mattiello, A., Molina-Montes, E., Nilsson, P.M., Overvad, K., Perquier, F., Redondo, M.L., Ricceri, F., Rolandsson, O., Romieu, I., Roswall, N., Scalbert, A., Schulze, M., Slimani, N., Spijkerman, A.M., Tjønneland, A., Tormo, M.J., Touillaud, M., Tumino, R., A.D.L., v.d., van Woudenberg, G.J., Langenberg, C., Riboli, E. and Wareham, N.J., 2014. Dietary intakes of individual flavanols and flavonols are inversely associated with incident type 2 diabetes in european populations. *J. Nutr.* 144, 335-343.

Legends to Figures

Figure 1. Chemical structure of main flavanols. (A) Flavanol monomers. (B and C) Procyanidins.

Table 1.- Epidemiologic studies of the association between tea consumption and T2D.

Study	Participants	Association with T2D	Reference
European Investigation into Cancer and Nutrition (EPIC)	38,176	≥ 4 cups of tea/day reduced in a 42% the risk of T2D	(van Dieren, S. et al., 2009)
National Health and Nutrition Epidemiologic Follow Up Study (NHEFS)	14,407	Regular consumption of tea was associated with a decreased risk of diabetes in non-elderly adults (≤ 60 years) who had lost weight	(Greenberg, J.A. et al., 2005)
Mediterranean Islands (MEDIS) study	542	Inverse association between tea consumption (1-2 cups/day) and fasting glucose levels in non-obese elderly	(Polychronopoulos, E., et al., 2008)
Japan Collaborative Cohort (JACC) Study	17,413	Consumption of green tea rather than black and oolong teas was associated with T2D risk reduction	(Iso, H., et al., 2006)
Women's Health Study (WHS)	38,018	Green tea intake (≥ 4 cups/day) was modestly related with a reduced risk of diabetes. In non-diabetic women total intake of flavonols and flavones was not associated with levels of fasting Ins, HbA1c, CRP or IL-6	(Song, Y., et al., 2005)
Singapore Chinese Health Study	36,908	Regular consumption of black tea but not green tea decreased T2D risk in Asian men and women	(Oodegaard, A.O. et al., 2008)
Whitehall cohort	10,308	Moderate tea drinking (≥ 3 cups/day) was not associated to a decreased incidence of T2D. A combined effect of coffee and tea was reported	(Hamer, M. et al., 2008)
Takayama cohort (Japan)	31,152	No relationship between tea intake and risk of diabetes	(Oba, S. et al., 2010)
High-risk and Population Strategy for	4,975	Long-term high oolong tea consumption (≥ 2	(Hayashino, Y. et al., 2011)

Occupational Health Promotion Study (HIPOP-OHP)		cups/day) increased the risk of T2D (enhanced fasting glucose levels) in men	
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CRP: C-reactive protein; **HbA1c:** glycated haemoglobin; **IL-6:** interleukin-6.

Table 2.- Human interventional trials of the effects of tea intake in diabetic patients^a

Design	Participants	Duration (weeks)	Dose (day)	Effects	Reference
Case-control	100 healthy and 100 diabetic	≥ 52	≥ 1 cup/week	Protective effect on retinopathy in women, not in men	(Ma, Q et al., 2015)
Double-blind controlled	43 diabetic	12	340 mL (green tea group, 582.8 mg catechins; control, 96.3 mg catechins)	↓ waist circumference, ↑ adiponectin, = Gluc, = HbA1c, ↑ Ins	(Nagao, T., et al., 2009)
Randomized controlled	63 diabetic	8	0, 2, 4 cups/day (2.5g green tea in 200 mL per cup)	↓ systolic BP, ↓ BW, ↓ BMI, ↓ waist circumference, = Gluc, = Ch, = TG, = HDL, = LDL, = ApoA1, = ApoB100, = MDA, = TAC	(Mousavi, A et al., 2013)
Randomized controlled	100 hypertensive diabetic	4	150 mL, 3 times/day (3 g green tea in 150 mL per cup)	↓ systolic BP, ↓ diastolic BP	(Mozaffari-Khosravi, H. et al., 2013)
Randomized, double-blinded, and placebo-controlled	92 diabetic	16	500 mg decaffeinated GTE or cellulose, 3 times/day	↓ TG, ↓HOMA-IR, ↑ HDL, ↑ adiponectin, ↑ ApoA1, ↑ ApoB100, ↑ GLP-1	(Liu, C.-Y. et al., 2014)
Randomized double-blinded controlled	42 diabetic	12	200 mg GTP, 4 times/day	↓ UACR	(Borges, C.M. et al., 2016)
Randomized, double-	72 diabetic	8	500 mg GTE or	↓ Gluc, ↓ Ins, ↓ HbA1c, ↑ bone turnover	(Mirzaei, K. et al., 2009)

blinded, and placebo-controlled			cellulose, 3 times/day		
Randomized controlled	46 diabetic	4	150-600 mL/day (1-4 cups black tea/day, 2.5 g tea/cup)	↓ MDA, ↓ CRP, ↑ GSH	(Nesyestani, T.R. et al., 2010)
Randomized controlled	36 diabetic	12	200-600 mL/day (1-3 cups black tea/day, 2.5 g tea/cup)	↓ HbA1c, ↓ Ch, ↑ CD3+, ↑ CD4+, ↑ CD25+, ↑ FOXP3, ↑ CD3+, ↑ ↑ CD4+, ↑ IL-10+, ↓ CD3+, ↓ CD4+ ↓, IL-17+, ↓ Th1-associated CD3+ CD4+ IFN-γ+	(Mahmoud, F. et al., 2016)
Randomized crossover	20 diabetic	4	1,500 mL/day (15 g oolong tea divided in 5 times/day)	↓ Gluc, ↓ fructosamine	(Hosoda, K. et al., 2003)
Randomized crossover	55 diabetic	4	900 mL green tea/day (9 g tea)	= Gluc, = Ins, = Ch, = LDL, = HDL, = TG, = insulin resistance, = adiponectin, = CRP, = IL-6, = brachial-ankle pulse wave velocity	(Ryu, O.H. et al., 2006)
Randomized controlled	66 diabetic	8	500 mg GTE, 2-3 times/day	= BW, = BMI, = systolic and diastolic BP, = Gluc, = HbA1c, = Ins, = HOMA-IR	(Fukino, Y. et al., 2005)
Randomized, double-blinded, and placebo-controlled	68 obese diabetic	16	1,500 mg GTE	= HbA1c, = waist circumference, = HOMA-IR, = Ins, ↑ ghrelin	(Hsu, C.H. et al., 2011)
Randomized double-blinded controlled	49 diabetic	12	375-750 mg theaflavins or 375 mg cellulose	= HbA1c	(MacKenzie, T. et al., 2007)

^a The arrow indicates an increase (↑) or decrease (↓) in the levels or activity of the different parameters analysed. “=” symbol designates unchanged parameters.

Apo: apolipoprotein; **BMI:** body mass index; **BP:** blood pressure; **BW:** body weight; **Ch:** Total cholesterol; **CD:** T lymphocytes with the immunophenotype CD; **CRP:** C-reactive protein; **FOXP3:** forkhead box P3; **GLP-1:** glucagon-like peptide 1; **Gluc:** glucose; **GSH:** glutathione; **GTE:** green tea extract; **GTP:** green tea polyphenols, **HbA1c:** glycated haemoglobin; **HDL:** high-density lipoprotein; **HOMA-IR:** homeostatic model assessment of insulin resistance; **IFN-γ:** interferon-γ; **IL:** Interleukin; **Ins:** Insulin; **LDL:** low-density lipoprotein; **MDA:** malondialdehyde; **TAC:** total antioxidant activity; **TG:** Triglyceride; **UACR:** urinary albumin-creatinine ratio.

Table 3.- Epidemiologic studies of the association between moderate wine consumption and the development of T2D.

Study	Participants	Association with T2D	Reference
Melbourne Collaborative Cohort Study (MCCS)	36,527	Alcohol from wine was associated with reduced risk of T2D	(Hodge, A.M. et al., 2006)
European Investigation into Cancer and Nutrition (EPIC)–InterAct	26,088	Wine or fortified wine consumption appeared to be most strongly associated with a reduced risk of diabetes	(Beulens, J.W. et al., 2012)
Stockholm Diabetes Prevention Program (SDPP)	11,819	Moderate wine consumption is associated with a reduced risk of T2D in woman	(Cullmann, M. et al., 2012)
Nord-Trøndelag Health Survey (HUNT) study	90,296	Consumption of wine rather than of beer and spirits was associated with T2D risk reduction	(Rasouli, B. et al., 2013)
Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale (E3N)-EPIC	66,485	Wine drinking is inversely associated with T2D risk in overweight women	(Fagherazzi, G. et al., 2014)
Caucasian population of Lausanne (Switzerland) study (Colaüs Study)	4,765	Small protective effect of wine consumption on T2D	(Marques-Vidal, P. et al., 2015)
Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial	11,140	Moderate wine drinking presented decreased risks of cardiovascular accidents and micro vascular complications in T2D patients	(Blomster, J.I. et al., 2014)

Table 4.- Human interventional trials of the effects of wine consume in T2D patients^a

Design	Participants	Duration (weeks)	Dose (day)	Effects	Reference
Parallel treatment	17 diabetic	2	180 mL of red wine	= Ins, = Gluc, = HbA1c, = BMI, = Ch, = TG, ↑ insulin sensitivity, = FBF	(Napoli, R. et al., 2005)
Randomized crossover	52 healthy and 16 diabetic	4	100 mL red wine or dealcoholized red wine	= Ins, = Gluc, = Ch, = TG, ↓ LDL ↓ HOMA-IR,	(Chiva-Blanch, G. et al., 2014)
Randomized controlled	109 diabetic	12	150 mL of red or white wine	↓ Gluc, ↓ HbA1c, = TG, = HDL, ↓ LDL, ↓ waist circumference	(Shai, I. et al., 2007)
Randomized crossover	17 diabetic	4	120 to 240 mL of red or white wine	↓ Ins, = Gluc, = HbA1c, = BMI, = Ch, = TG, = HDL, = LDL	(Bantle, A.E. et al., 2008)
Randomized controlled	115 diabetic	48	118 mL of red wine	= Gluc, = BMI, = Ch, = TG, ↓ HDL, ↓ TNF-α, ↓ IL-6, ↓ CRP	(Marfella, R., et al. 2006)
Randomized controlled	224 diabetic	96	150 mL of red or white wine	↓ Gluc, = HbA1c, = Ch, ↑ HDL, ↓ HOMA-IR	(Gepner, Y. et al., 2015)
Randomized controlled	224 diabetic	96	150 mL of red or white wine	↓ Gluc, = HbA1c, = Ch, ↑ HDL, ↓ HOMA-IR, ↓ VAT	(Golan, R. et al. 2016)

^a The arrow indicates an increase (↑) or decrease (↓) in the levels or activity of the different parameters analysed. “=” symbol designates unchanged parameters.

BMI: body mass index; **Ch:** Total cholesterol; **CRP:** C-reactive protein; **FBF:** Forearm blood flow; **Gluc:** glucose; **HbA1c:** glycated haemoglobin; **HOMA-**

IR: homeostatic model assessment of insulin resistance; **Ins:** Insulin; **IL-6** Interleukin-6; **LDL:** low-density lipoprotein; **TG:** Triglyceride; **TNF- α :** Tumor Necrosis Factor-alpha; **VAT:** Visceral adipose tissue accumulation.

Table 5.- Human interventional trials of the effects of chocolate intake in healthy and T2D patients^a.

Design	Participants	Duration (days)	Dose (day)	Effects	Reference
Randomised placebo-controlled	15	15	Dark chocolate (500 mg polyphenols/day)	↓ HOMA-IR, ↓ BP, ↓ LDL, = Ins	(Grassi, D. et al., 2005a)
Randomised	20	15	Dark chocolate (88-150 mg flavanols/day)	↓ HOMA-IR, ↑ Ins sensitivity, ↓ BP, ↑ beta cell function	(Grassi, D. et al., 2005b) (Grassi, D. et al., 2008)
Randomized, placebo-controlled double-blind crossover	12	56	High-polyphenol chocolate (50 mg EC)	= HOMA-IR, = BP, ↑ HDL, = Gluc, = Ins, = HbA1c	(Mellor, D.D. et al., 2010)
Randomised placebo-controlled cross-over	42	28	Dark chocolate (500 mg day)	↓ BP, ↓ HOMA-IR, ↓ fasting Gluc	(Almoosawi, S. et al. 2012)
Randomized, double-blind, controlled	93	365	High flavanol chocolate (850 mg flavanols day)	↓ HOMA-IR, ↓ Ins, ↑ HDL, ↓ risk CV disease	(Curtis, P.J. et al., 2012) (Curtis, P.J. et al., 2013)
Randomized, placebo controlled, double-blind	60	56	High-polyphenol chocolate (450 mg flavonoids)	↓ BP, ↓ HbA1c, ↓ fasting Gluc	(Rostami, A. et al., 2014)

^a The arrow indicates an increase (↑) or decrease (↓) in the levels or activity of the different parameters analysed. “=” symbol designates unchanged parameters. **BP**: blood pressure; **CV**: cardiovascular; **Gluc**: glucose; **HbA1c**: glycated haemoglobin; **HDL**: high-density lipoprotein **HOMA-IR**: homeostatic model assessment of insulin resistance; **Ins**: Insulin.

Table 6.- Human interventional trials of the effects of cocoa intake in healthy and T2D patients^a.

Design	Participants	Duration (days)	Dose (day)	Effects	Reference
Randomized	49	84	High flavanol cocoa (902 mg/day)	↑ endothelial function, ↓ cardiometabolic risk factors	(Davison, K. et al., 2008)
Pilot study	5	90	Cocoa powder (100 mg EC/day)	↑ GSH, ↑ SOD2, ↑ CAT	(Ramírez-Sánchez, I. et al., 2013)
Randomised, controlled, cross-over, free-living	44	28	Cocoa powder (416 mg polyphenols/day)	↑ HDL, ↓ fasting Gluc, ↓ IL-1β, ↓ IL-10	(Sarriá, B. et al., 2014)
Randomized clinical control trial	100	42	20 g cocoa powder/day	↓ LDL, ↓ TG, ↓ Cho, ↓ CRP, ↓ IL-6	(Parsaeyan, N. et al., 2014)
Randomized, crossover trial	18	6h postprandial	Cocoa beverage (960 mg polyphenols/day)	↑ HDL, = IR, ↑ Ins	(Basu, A. et al., 2015)
Randomized, placebo-controlled, double-blind, crossover trial	20	14	Cocoa beverage (900 mg flavanols/day)	= BP, = glycemic parameters	(Muniyappa, R. et al., 2008)
Randomized, double-	41	30	Flavanol-rich cocoa	= glycemic parameters, = BP	(Balzer, J. et al., 2008)

masked fashion			(963 mg flavanols/day)		
Randomized crossover design	20	5	Cocoa beverage (900 mg flavanols/day)	= glycemic parameters, = IL-6, = CRP	(Stote, K.S. et al., 2012)

^aThe arrow indicates an increase (↑) or decrease (↓) in the levels or activity of the different parameters analysed. “=” symbol designates unchanged parameters. **BP**: blood pressure; **CAT**: catalase; **CRP**: C-reactive protein; **Gluc**: glucose; **GSH**: glutathione; **HDL**: high-density lipoprotein; **IL**: interleukin; **Ins**: Insulin; **IR**: insulin resistance.

Figure 1