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Review

Coffee consumption and human health – beneficial or detrimental? – Mechanisms for effects of coffee consumption on different risk factors for cardiovascular disease and type 2 diabetes mellitus

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Coffee is probably the most frequently ingested beverage worldwide. Especially Scandinavia has a high prevalence of coffee-drinkers, and they traditionally make their coffee by boiling ground coffee beans and water. Because of its consumption in most countries in the world, it is interesting, from both a public and a scientific perspective, to discuss its potential benefits or adverse aspects in relation to especially two main health problems, namely cardiovascular disease and type 2 diabetes mellitus. Epidemiological studies suggest that consumption of boiled coffee is associated with elevated risk for cardiovascular disease. This is mainly due to the two diterpenes identified in the lipid fraction of coffee grounds, cafestol and kahweol. These compounds promote increased plasma concentration of cholesterol in humans. Coffee is also a rich source of many other ingredients that may contribute to its biological activity, like heterocyclic compounds that exhibit strong antioxidant activity. Based on the literature reviewed, it is apparent that moderate daily filtered, coffee intake is not associated with any adverse effects on cardiovascular outcome. On the contrary, the data shows that coffee has a significant antioxidant activity, and may have an inverse association with the risk of type 2 diabetes mellitus.

Keywords: Antioxidant / Coffee / Coronary heart disease / Review / Type 2 diabetes mellitus

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Abbreviations: DM, diabetes mellitus; **LDL**, low-denisty lipoprotein; **oxLDL**, oxidatively modified LDL; **PPAR**, peroxisome proliferator activated receptor, **VLDL**, very low density lipoprotein

1 Introduction

The name coffee is derived from the name of the province Keffa where shepherds from Abyssinia/Ethiopia discovered the coffee beans in the 6th century. In the 13th century coffee's restorative powers were known and spread throughout the Islamic word. Two hundred years later coffee was sold in Europe, thus introducing the new beverage into Western life and custom [1]. The popularity of coffee as a beverage is ever increasing, despite the fact that there are reports that it is not necessarily good for your health. Historically, coffee consumption has frequently been related to unhealthy behaviors, such as smoking, excessive consumption of alcohol, a poor diet, and a sedentary lifestyle. However, recent knowledge has put coffee in a more positive light, and to

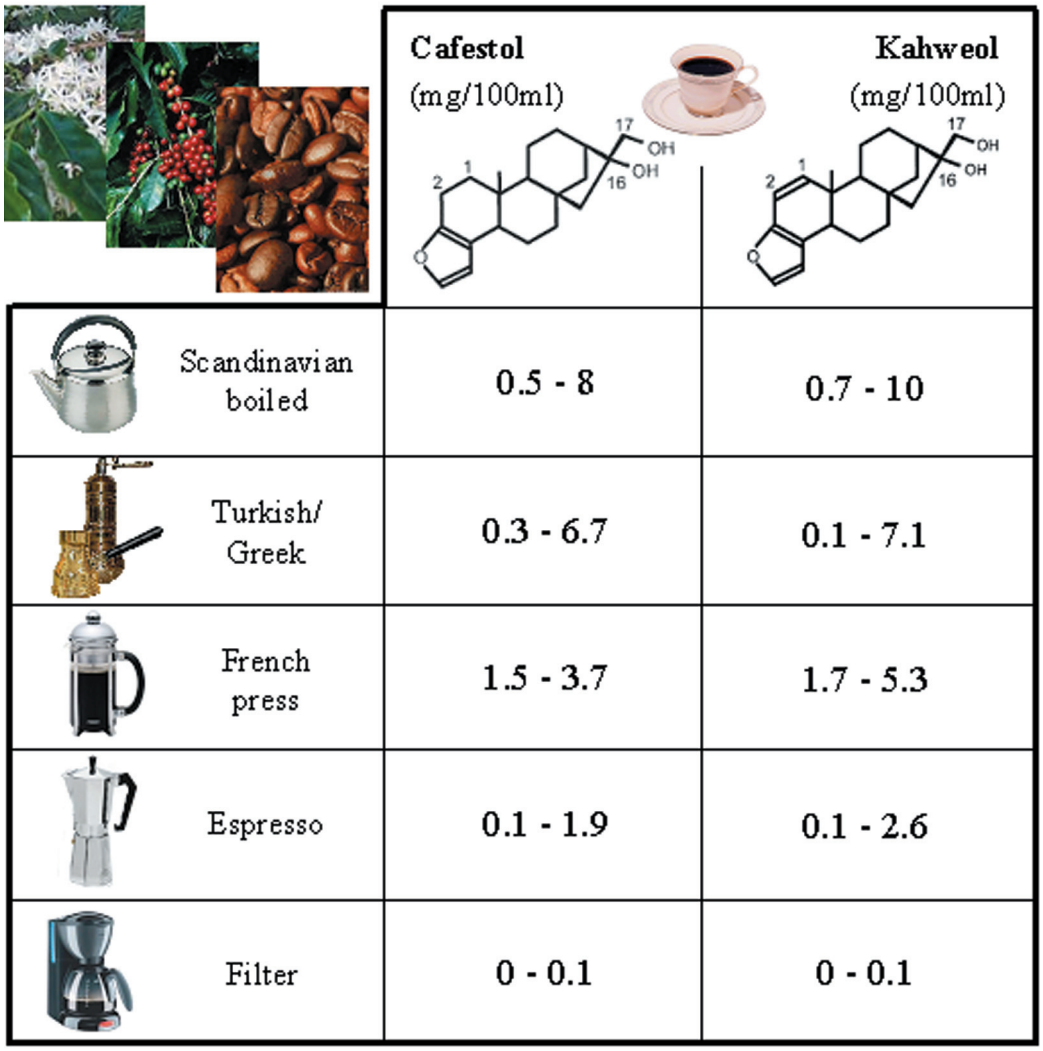

Figure 1. Content of coffee diterpenes, cafestol and kahweol, in different types of coffee brews.

date there are data suggesting that coffee consumption have beneficial effects on human health. Within Europe, coffee is most popular in Scandinavian countries, Austria, and the Netherlands. Almost 10 kg of coffee per capita per year is consumed in Norway, and this is twice as much as an average per capita consumption in Europe, according to the International Coffee Organization (ICO).

The purpose of this review is to provide an overview of the relationship between coffee consumption and human health, with a special emphasis on cardiovascular disease. There is, however, a growing interest in the positive biological properties of coffee ingestion, among these the antioxidant effect and the recently published inverse relationship of coffee consumption and type 2 diabetes mellitus, which also will be debated. We will briefly comment on some of the epidemiological data, and present some studies from our own laboratory, where we mainly examined the effect of two diterpenes in coffee, cafestol and kahweol, on mechanisms known to be involved in the regulation of lipid homeostasis. Finally, the clinical implications of these results will be discussed.

2 Coffee constituents

Coffee contains a multitude of substances, many of which are potentially biologically active. Two diterpenoid alcohols, cafestol and kahweol, are found at significant levels in coffee (Fig. 1). They are natural constituents of coffee beans [2], and are released from roast and ground coffee beans by hot water, but are largely trapped by the use of a paper filter in coffee preparation. These components have been identified as hypercholesterolemic, but although the diterpenes are retained in the filter, there is some evidence that consumption of filtered coffee is associated with a risk of cardiovascular disease [3].

Caffeine is a natural alkaloid found in coffee beans, tea leaves, cocoa beans, and other plants. Coffee has both the highest and the most variable caffeine content among dietary products containing this alkaloid [4]. It is suggested that values differ from 30–175 mg of caffeine per cup (150 mL) coffee [5]. The standard value has been suggested to be 85 mg of caffeine per cup of ground roasted coffee [4]. Caffeine present in coffee can cause addiction and stimulate the central nervous system. There are publications that indicate that caffeine has an effect on the cardiovascular system with a slight increase in blood pressure and a modest decrease in heart rate. Some of the effects of caffeine, such as those on the heart and blood vessels, are inconsistent, and may only be noticeable when regular consumers suddenly cut out caffeine [6–8]. Coffee is also a rich source of many other ingredients that may contribute to its biological activity. For example, coffee contains a substantial amount of potassium, niacin, magnesium- and antioxidant substances, such as tocopherols and phenol chlorogenic acid (the ester of caffeic acid and quinic acid) [9, 10].

3 Epidemiological studies

3.1 Serum cholesterol levels and cardiovascular risk

A number of studies have examined the association between boiled coffee consumption and cardiovascular disease. There is good evidence that nonfiltered, boiled coffee increases the serum cholesterol level, and thus increases the coronary heart disease [11, 12]. Two decades ago, Thelle *et al.* [13] reported a positive correlation between the amount of coffee ingested and serum cholesterol levels in a population-based study in Northern Norway. Although these findings were confirmed in several subsequent studies [14–16], other studies have not shown a cholesterol-raising effect of coffee consumption [17]. It was later shown that the method of brewing was an important factor for the hypercholesterolemic effect of coffee. In contrast to boiled coffee, consumption of filtered coffee was found to have little or no association with serum concentration of cholesterol [18–21]. The brewing releases oil droplets containing diterpenes from ground coffee beans, and the oil is retained by a paper filter. The diterpene content varies according to the principles for brewing (Fig. 1) [22].

Most studies of diet and cholesterol response have been carried out in men, and it is not known whether women react to diet to the same extent as men do. Therefore, Weggemans *et al.* [23] studied sex differences in the response of serum cholesterol and lipoproteins to diet. Interestingly, they found that responses of total and low-density-lipoprotein (LDL)-cholesterol to cafestol were larger in men than in women, and this was not due to their larger overall food intake. The authors suggested that sex hormones could affect the different response.

There are, however, studies revealing that coffee may have a positive influence on human health. In a Scottish population of men and women increasing coffee consumption was associated with beneficial effects on mortality and coronary morbidity [24]. In this study, coffee drinking was associated with affluent and cosmopolitan lifestyle, which the author meant could be explained by residual confounding factors. Other studies have also shown a positive effect of coffee drinking on mortality [25, 26].

3.2 Homocysteine

An elevated plasma homocysteine concentration is a risk factor for cardiovascular disease [27]. A positive correlation between plasma homocysteine concentration and coffee consumption was reported in several studies [28, 29]. In Norway, 12 000 heavy coffee-drinking men and women were studied [30]. They found that coffee consumption was a major lifestyle determinant of plasma homocysteine distribution in a large, healthy population. An important question is whether this effect on plasma homocysteine was caused by factors present in both unfiltered and filtered coffee. Urgert *et al.* [31] showed that daily consumption of paper-filtered coffee for 4 weeks significantly raised the plasma concentration of total homocysteine in healthy subjects. Another study raised the question whether caffeine explains the homocysteine-raising effect of coffee [29]. The subjects were given capsules of caffeine, paper-filtered coffee, or placebo capsules. This study indicated that coffee treatment increased the homocysteine concentration by 11% compared with placebo, while caffeine treatment had a weaker acute effect on homocysteine (5% increase). They concluded that caffeine was partly responsible for the homocysteine-raising effect of coffee. A study by Grubben *et al.* [32] showed that unfiltered coffee increases plasma homocysteine concentration by 10% in subjects who drank six cups of unfiltered coffee per day for 2 weeks. Concentrations of vitamin B12 and folate in plasma were not found to be changed between the intervention periods, but the vitamin B6 concentration decreased during the coffee period. They speculated that the effect of coffee on homocysteine concentrations could be due to a decrease in blood vitamin B6 concentration mediated by caffeine. In contrast to most studies, a recent report showed that moderate coffee consumption among healthy subjects did not significantly increase the homocysteine level, even though a tendency was observed [33].

3.3 Antioxidants

Depending on the brewing methods, over 100 different active chemicals have been identified [34]. Among coffee

constituents the lipid-soluble heterocyclic compounds, including furans, pyrroles, and maltol, have been found to exhibit higher antioxidant function, compared to the aqueous solution [1]. Melanoidins exhibit strong antioxidant activity [35], and inhibited significantly lipid oxidation [36, 37]. These are formed during roasting of coffee beans [38]. When coffee drinks were examined for antioxidant properties, measured as DNA-protection through quenching of hydroxyl radical generating systems, caffeine and its metabolites, theobromine and xanthine, appeared to possess strong DNA-protective effects [39].

Caffeine and polyphenolic compounds that are present in relatively high levels in the plant beverages, including chlorogenic acids and their degradation products, have been considered as good candidates for a protective effect/role of coffee [40, 41]. Svilaas *et al.* [42] determined the contribution of various food groups to total antioxidant intake in humans, measured by a FRAP (ferric reducing ability of plasma) assay, and assessed the correlation of the total antioxidant intake from the food groups with plasma antioxidants. Surprisingly, they observed that the single greatest contributor to the total antioxidant intake was coffee (approximately 66%). The authors suggested that chlorogenic acid is probably responsible for a substantial part of the antioxidant effect of coffee. Another study examined the antioxidant capacity of plasma before and after supplementation with filter brewed coffee, and the authors reported that the increase they measured in plasma antioxidant capacity after supplementation, was probably linked to phenolic compounds in the brew [43]. Consumption of coffee may therefore prevent diseases by antioxidative effects.

3.4 Diabetes mellitus

Because type 2 diabetes mellitus is common and has serious complications, it is important to understand factors associated with the disease. Caffeine has been shown to reduce sensitivity to insulin [44], while in contrast chlorogenic acid present in coffee, reduces plasma glucose concentration [45]. A study in the Netherlands reported that people who drank at least seven cups of coffee a day were half as likely to develop type 2 diabetes mellitus as people who drank two cups or less a day [46]. Likewise, a long-term study on consumption of regular coffee, decaffeinated coffee, and other caffeinated beverages, suggested an inverse relationship between intakes of caffeine and regular coffee and incidence of diabetes in both men and women [47]. This relationship was stronger in women than in men. The researchers did not find a relationship between decaffeinated coffee intake and type 2 diabetes mellitus. Recently, Rosengren *et al.* [34] reported that more than two cups of coffee per day had potentially beneficial effects and protected from the development of diabetes in Swedish women. Their study comprised a random population sample of 1361 women over 18-years follow-up. Even though this study was limited in size, the data indicated that some components in coffee may have a protective effect with respect to the development of diabetes in women, and this supports the findings of the large-scale, prospective cohorts of van Dam [46], Tuomilehto [48], and Salzar-Martinez [47]. In contrast, short-term metabolic studies have shown that caffeine ingestion can acutely decrease insulin sensitivity [44] and glucose disposal [49]. Van Dam *et al.* [50] examined the effects of coffee and caffeine on fasting blood glucose and insulin over 2–4 weeks in healthy subjects. They reported that high coffee consumption for 4 weeks increased fasting insulin concentrations compared to no coffee intake. Consumption on weaker coffee did not significantly verify this association. The authors suggested that the increased fasting insulin concentrations reflected decreased insulin sensitivity. No effect on fasting glucose concentrations was observed.

4 Underlying mechanisms

4.1 Mechanisms of coffee consumption involved in cardiovascular disease

Even though convincing epidemiological data shows a positive relationship between intake of coffee and plasma lipid levels, the mechanism of how coffee causes such effects are still unclear. However, after the identification and purification of the lipid raising diterpenes (cafestol and kahweol) from coffee beans [11, 12], we and others have put efforts into studying their mechanisms of action in different cell types. In our experimental setting we used the purified coffee diterpenes in a concentration presumably achievable after moderate to high intake of unfiltered coffee.

So far, mechanistic studies in tissue cultures have been inconsistent after stimulation with either cafestol or kahweol, or a combination of these. While human skin fibroblasts (HSFs) showed a reduced LDL uptake and binding through mechanism presumably independent of reduced gene expression of LDL receptor [51], human intestinal cells (CaCo-2) enhanced the LDL uptake through an increased LDL receptor gene expression [52]. Reporter gene experiments in CaCo-2 revealed that sterol regulatory element-1 (SRE-1) was activated by cafestol, but this was not the case in HSF. However, both intestine and fibroblasts are of less impact in lipid homeostasis *in vivo*, as compared to the liver, which is the major site of lipid metabolism. Therefore, our work in the human liver cell line HepG2, accompanied with data from the HSF study, is of particular importance. Interestingly, our study revealed that two crucial key actors in cholesterol metabolism; LDL receptor and acyl-CoA : cholesterol ester transferase (ACAT) were down-regulated and up-regulated by cafestol in HepG2

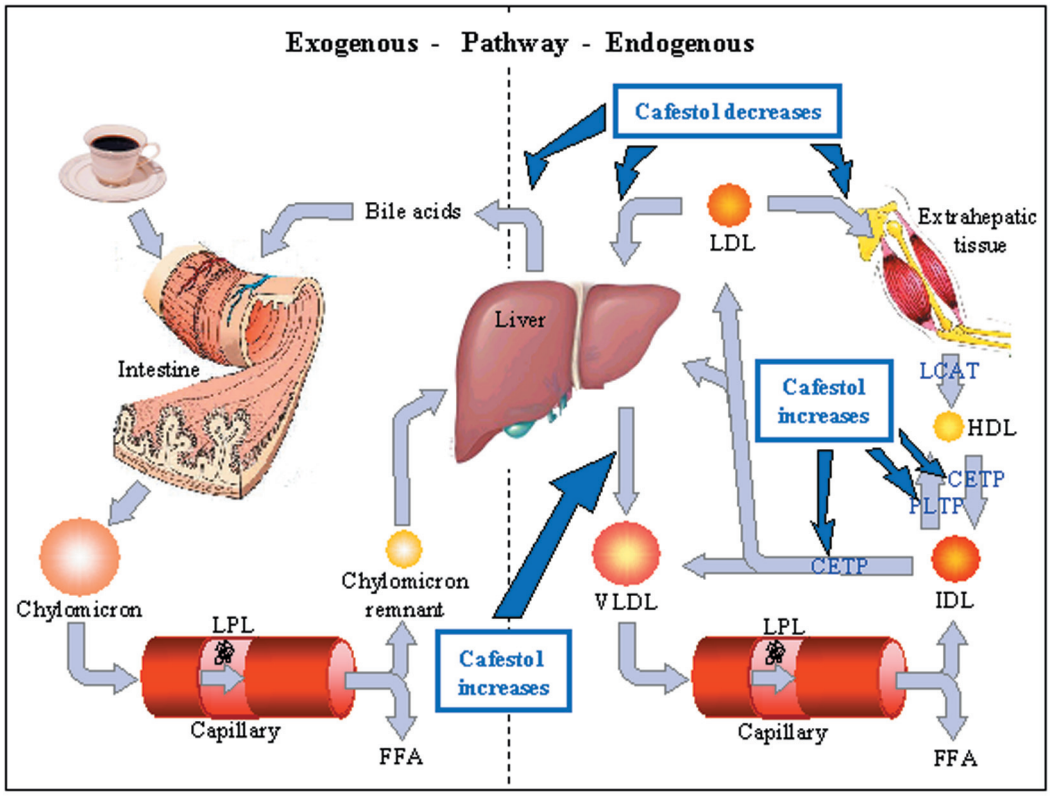

Figure 2. Current understanding of cafestol-mediated effects on lipid homeostasis. Data are based on human and animal *in vivo* and *in vitro* studies. LDL, low density lipoprotein; CETP, cholesterol ester transfer protein; PLTP, phospholipid transfer protein; LPL, lipoprotein lipase; VLDL, very low density lipoprotein; HDL, high density lipoprotein; IDL, intermediate density lipoprotein; HL, hepatic lipase; LPL, lipoprotein lipase; FFA, free fatty acids; LCAT, lysolecithin:cholesterol acyltransferase.

cells [53] and HSF [51], respectively. Moreover, the HMG-CoA reductase activity and bile acid synthesis, have been reported suppressed in cafestol fed transgenic mice (apoE-Leiden) (see below) [54]. Taken together (see summary in Fig. 2) these results, and in particular those from liver studies, may explain why plasma cholesterol rises in humans after intake of coffee or other coffee beverages. The apparent inconsistency in mechanism of action between the cell types could be explained by the difference in metabolic function, and potential metabolites may be derived during catabolism causing different effects in various cell types. These results may at least partly explain the cholesterol raising effect seen in human after intake of coffee or other coffee beverages even though the mechanisms seem to be multiple and cell specific.

Animal and human investigations have followed up our mechanistic studies in cell cultures. Some years ago, a Dutch group reported that genetic polymorphisms in the apoE gene in normolipidemic subjects responded differently to cafestol, suggesting that genetic predisposition may determine the response to lipid intake [55]. Another study among eight normolipidemic subjects, which were given 75 mg cafestol daily for 2 weeks (comparable to ~ten cups of Scandinavian-type boiled coffee per day) showed an ~30% increased triacylglycerol secretion of apoB-enriched very-low-density lipoprotein (VLDL) particles, accompanied by reduced catabolic rate of VLDL [56]. Cafestol as a potent inducers of abnormal lipid levels in human is clearly demonstrated by this study (see Fig. 2).

Cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) have been reported to increase after long-term (24 weeks) intake of French press coffee (0.9 L/day) in normolipidemic subjects [57]. The authors claimed that this increase in CETP could precede the LDL cholesterol rise seen in humans after cafestol and kahweol intake. The triacylglycerol rise, found in the study, was only transient. The latter observation could be explained by an adaptive mechanism in lipid metabolism, which is still poorly understood. Moreover, in line with this human study, the same authors reported from a study in transgenic mice (apoE-Leiden) that cafestol suppressed the synthesis of bile acids (*via* reduced sterol 27-hydroxylase and oxysterol 7a-hydroxylase) along with reduced hepatic LDL receptors. The reduction of LDL receptors was followed by augmented cholesteryl ester-enriched VLDL particles without changes in plasma or VLDL triacylglycerol [54]. This

marked cholesteryl ester-enrichment of VLDL could in fact be mediated by a cafestol-induced effect on CETP, as reported from the human study [57]. Even more important, the pronounced effect on the bile acid synthesis seen in the cafestol treated mice might implicate human lipid metabolism and be the cholesterol-rising effects observed in humans after intake of coffee beverages.

In a comprehensive review de Roos and Katan [58] proposed some years ago several mechanisms by which cafestol may act on serum lipids. The mechanisms of most interest described by these authors are sterol-regulatory element binding proteins (SREBPs), CETP/PLPT, and peroxisome proliferator activated receptor (PPARs). Despite some inconsistencies, it is plausible that CETP and PLTP are involved in the cholesterol (LDL-cholesterol) and triacylglycerol (VLDL) raising effects seen in human. Both CETP and PLTP are involved in shuffling and redistribution of lipids between VLDL, LDL, and high-density lipoprotein (HDL) (see Fig. 2). From reporter gene analysis, however, it is unlikely that PPARα, β, and γ are implicated in the cafestol-mediating effects, as discussed by de Roos and Katan [58]. So far, SREBP-mediated signalling is presumably the pathway of most interest. In general, SERBP seems to be a key regulator in both cholesterol (*i.e.*, LDL receptor- and cholesterol- synthesis) and triacylglycerol metabolism (*i.e.*, fatty acid synthesis and lipoprotein lipase) [59].

An animal model in which coffee diterpenes similarly increase LDL-cholesterol would allow mechanistic studies that otherwise could not be done in humans. The effect of cafestol and kahweol on lipoprotein metabolism in monkeys, hamsters, rats, and gerbils was found to be different from that in human subjects [60]. The author concluded that studies on the mechanism of action should preferably be done in human subjects. This diverse effect of coffee diterpenes among animal species makes cafestol and kahweol exceptional. As far as we know, cafestol is the first nutrient with such divergent effects among animal species, including humans. Extensive metabolism of cafestol and kahweol has been reported from a study in ileostomy volunteers [61], which may suggest that the observed discrepancies indicate that the diterpenes are differently metabolised among animal species. As nicely reviewed by Terpstra *et al.* [62], it is apparent that mice, rats, monkeys, gerbils, and hamsters exhibit different lipid profiles after being fed with coffee diterpenes. On one side, data from studies in hamsters show large variations in plasma cholesterol, and on the other side, gerbils and monkeys are much less sensitive to coffee lipids than humans. In contrast, rats and humans have subsequently been shown to increase their lipid levels after intake of coffee diterpenes.

Notably, in view of the new knowledge of how nuclear receptor liver X receptors (LXRs) are involved in lipid homeostasis [63, 64], new studies in cell systems (*i.e.*, liver cells) and knockout mice should be conducted to clarify whether coffee lipids interact with the nuclear receptor family. Due to the fact that LXRs are reported to function as "cholesterol sensor" [65] it is of special importance. Intriguingly, available data suggest a SREBPs and LXRα cross-talk [63, 66]. It would have been valuable to study these *in vitro* and *in vivo* systems after cafestol stimulation. Such studies could at least partly clarify the molecular mechanisms executed by coffee diterpenes in more detail.

The development and progression of atherosclerosis is thought to be critically dependent on lipoprotein oxidation. Oxidative modification of LDL (oxLDL) by free radicals is one of the key and early events in the pathogenesis of atherosclerotic diseases [67]. Several dietary antioxidants have been shown to inhibit the oxidative modification of LDL, and, hence, have beneficial effects on atherogenesis *in vivo* [68, 69]. Recently, Yukawa *et al.* [70] conducted a study in healthy males of how coffee intake (24 g per day for one week) affected LDL oxidative susceptibility. These authors found that coffee consumption significantly reduced the susceptibility of LDL oxidation *ex vivo* measured as generation of conjugated dienes (lag time) and thiobarbituric acid reactive substances (TBARSs). This is in accordance to Richelle *et al.* [71] who investigated the relative antioxidant activity of coffee, tea, and cocoa using an *in vitro* LDL oxidation model. They found that all three beverages contained polyphenols with high antioxidant activities, the highest being soluble coffee. These studies indicate that regular coffee ingestion may favorably affect cardiovascular risk status by modestly reducing LDL oxidation susceptibility.

In the last decade, the homocysteine level has been reported to correlate positively to cardiovascular diseases [72], and as described above a positive correlation between the plasma homocysteine concentration and coffee consumption has been reported in several studies. Patients with inborn errors causing homocysteinuria (elevated plasma homocysteine/homocystine) develop premature cardiovascular and cerebovascular diseases [73]. The mechanisms involved, however, are still unclear. We reported some years ago that homocysteine in concentrations found in patients with homocysteinuria protects LDL towards Cu^{2+}-induced oxidation *in vitro* [74]. Other groups have shown that homocysteine enhances the oxidative stress of neutrophils [75] and the production of superoxide from endothelium [76]. Moreover, it has been speculated that the beneficial effects of folate found in epidemiological studies on homocysteine level can at least partly be explained by the capability folate has to scavenge free radicals generated through homocysteine oxidation. *In vitro* evidence demonstrates that 5-methyltetrahydrofolate, the main circulating metabolite of folate, can increase nitric oxide production and directly

scavenge superoxide radicals [77]. Interestingly, caffeine has been reported as a scavenger of hydroxyl radical at millimolar concentrations, whereas the antioxidant capacity at micromolar concentration is questionable [78]. Thus, folate, and presumably coffee-derived caffeine, may counteract the harmful effects of the coffee-induced rise of homocysteine as described above.

Glutathione (GSH) is an important endogenous antioxidant and cofactor of detoxifying metabolism, whereas γ-glutamylcysteine synthase (γ-GCS) is the rate limiting enzyme of GSH synthesis and an important regulator of endogenous antioxidant capacity. Recently, coffee diterpenes were found to increase the GSH and γ-GCS level in a hepatoma cell line in a dose-dependent manner [79] and hepatic GSH and GSH *S*-transferase (GST) activity in rats [80]. These data suggested that coffee diterpenes have chemoprotective effects through stimulation of the endogenous antioxidant system *via* a mechanism which presumably involves transcription factors, such as AP-1, Nrf2, and c-jun [81, 82]. In addition, a study by Esposito and co-workers [33] reported recently that moderate coffee consumption significantly increased the plasma GSH level among healthy subjects. There are, however, other factors than the lipophilic fraction of coffee brew that contribute to the overall antioxidant capacity. *N*-Methylpyridinium is such a factor, which is proven to enhance the plasma GST activity in rats [83]. Notably, coffee consumption is an exception in the way it displays dual antioxidant function. Firstly, coffee *per se* exhibits antioxidant properties, and secondly, coffee contains chemicals that turn on the endogenous antioxidant defence system.

4.2 Mechanisms of coffee consumption involved in diabetes mellitus

A good clinical description of diabetes mellitus (DM) is "a state of premature cardiovascular death which is associated with chronic hyperglycemia and may also be associated with blindness and renal failure" [84]. In such a complex condition several pathophysiological mechanisms are concerted. Among several highly relevant hypothesis the response-to-retention of early atherogenesis is one of the most intriguing [85]. Briefly, response-to-retention hypothesis holds that a key pathogenic event is an extracellular retention (or trapping) of cholesterol-rich, atherogenic lipoproteins within the subendothelial region of the arterial wall. Once retained, these lipoproteins undergo enzymatic and oxidative modification generating biologically active products (*i. e.*, oxLDL, oxysterols, lipid peroxides) that provoke local inflammation, recruitment of inflammatory cells (*i. e.*, monocytes/macrophages, T-cells) and generation of fat laden macrophages, thereby resulting in lesion progression. DM is thought, and partly proven, to enhance the response-to-retention cascade [86]. Especially, long-term effects of high blood glucose resulting in advanced glycosylated products, such as advanced glycation end products (AGEs) have been proven to accelerate the inflammatory response [87] and to enhance lipid accumulation of macrophages [88]. How coffee intake or coffee constituents contribute to pathophysiological processes like that of type DM is still unclear.

Among several risk factors associated with type II DM is small dense LDL [89]. This type of lipoprotein particle is readily oxidized and has high affinity for the extracellular matrix, and therefore prone to be retained within the vessel wall [90]. Another risk factor connected to DM is 8-isoprostane [91], which is a marker of oxidative stress *in vivo* [92]. The major source of this active lipid is oxidized LDL [93], and we have recently published data indicating that 8-isoprostane is a key actor in atherogenesis [94, 95]. It is therefore tempting to speculate that one of the benefits of coffee consumption, particularly in type II DM, is through reduced generation of free radicals due to the coffee-derived antioxidants, which subsequently cause a reduced generation of particular oxidized small dense LDLs.

The outcome of long-term coffee drinking has recently been found to lowering the risk of type 2 DM in several well-conducted studies [47]. Although the biological mechanism behind this inverse association between coffee consumption and the risk of type 2 DM is unknown, several putative mechanisms can be proposed. The coffee-protective mechanism could be effectuated through an inhibition of glucose-6-phosphatase [45]. Hepatic glucose-6-phosphatase is a key control site in the homeostatic regulation of blood glucose level [96], and reduced function of this enzyme may reduce plasma glucose concentration [45]. This unexpected and beneficial outcome of coffee consumption appears also to be coupled to caffeine. In contrast to acute administration of caffeine, long-term exposure seems to increase the insulin sensitivity [47]. In addition, caffeine has been shown to exhibit several biological effects, such as increased fat oxidation and mobilization of glycogen in muscle [97], increased lipolysis [98], and decreased body fat [99].

A new type of drug called PPARγ agonists, such as thiazolidinediones (TZDs) has shown promising results in treatment of type 2 DM. Among several favorable effects, TZD improves insulin sensitivity and reduces oxidative stress [100, 101] analogously to that reported from long-term studies with caffeine, even though a "causal-relation" is not yet proven. However, it is well-established that oxidative stress is involved in several pathological conditions including diabetes. Interestingly, Maziere *et al.* [102] reported recently that oxidized LDL not only is involved in atherosclerosis, but also inhibits insulin-signaling causing insulin

resistance, as observed in type 2 DM. Whether coffee lipids, such as cafestol and kahweol, affect the PPAR signaling, and in fact are actors in the insulin regulation, is at the present uncertain. There is evidence that coffee beverage consists of various antioxidants, which may attenuate the susceptibility of LDL to oxidative modification and accordingly improve the insulin sensitivity as previously reported [102]. All together, the burden of experimental evidence is that improved insulin sensitivity stabilizes glucose homeostasis, reduces AGE, enhances the blood lipid profile, and most likely inhibits atherogenesis [103, 104].

5 Conclusions

Coffee is one of the most interesting nutrients due to its multifaceted functions in human health (Fig. 3). On one side, coffee raises plasma lipids in humans, and on the other side coffee seems to exhibit antioxidant functions with beneficial outcome especially for type II DM. Even with the inconsistency in effects of coffee lipids on lipid homeostasis in different model systems (*i.e.*, cell cultures, animal models), the data obtained from human studies seem consistent. Intake of coffee lipids derived from coffee beans after brewing seems to be associated to increased plasma lipid levels presumably due to reduced clearance of cholesterol-rich lipoproteins concomitant with increased secretion of triacylglycerol-enriched lipoproteins (*i.e.*, VLDL). On the other hand, coffee consumption appears to facilitate the endogenous antioxidant system through increased γ-glutamylcysteine synthase (γ-GCS), and the proposed favorable effects seen in type II DM of coffee ingestion, is likely to involve several mechanisms probably driven by coffee-derived antioxidants. Accordingly, consumption of antioxidant-rich coffee may prevent diseases caused by oxidative injuries.

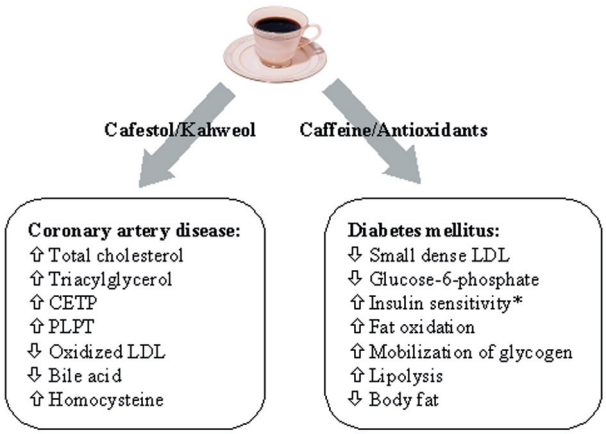

Figure 3. Summary of reported effects of coffee consumption on human health and certain risk factors. The asterisk indicates long-term coffee consumption. LDL, low density lipoprotein; CETP, cholesterol ester transfer protein; PLTP, phospholipid transfer protein.

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